

JPRS 71507

19 July 1978

TRANSLATIONS ON USSR SCIENCE AND TECHNOLOGY
BIOMEDICAL AND BEHAVIORAL SCIENCES
No. 37

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HEMATOLOGY

UDC 617-001.17-06:616.981.25-085.373.39

HYPERIMMUNE ANTISTAPHYLOCOCCUS PLASMA IN INTEGRATED THERAPY OF STAPHYLOCOCCUS INFECTION OF BURN VICTIMS

Moscow PROBLEMY GEMATOLOGII I PERELIVANIYA KROVI in Russian No 5, 1978 pp 27-31

[Article by Prof V. K. Sologub, Dr Biol Sci I. I. Kolker, Dr Med Sci G. F. Papko, Yu. M. Panova, I. A. Grishina, V. G. Pobedina, Ye. M. Makarova, and Z. N. Lukovkina, All-Union Burn Center, Laboratory of Microbiology and Immunology of the USSR Academy of Medical Sciences Institute of Surgery imeni A. V. Vishnevskiy, and USSR Ministry of Public Health Central Institute of Hematology and Blood Transfusion, Moscow]

[Text] An analysis of mortality in the 12 years of work of the All-Union Burn Center of the USSR Academy of Medical Sciences Institute of Surgery imeni A. V. Vishnevskiy showed that burn sepsis is the cause of death of 45 percent of the patients. Sepsis usually develops among patients with burn trauma during the period of septicemia (39 percent of the deceased patients (12)).

Staphylococcus associated with burn wounds is one of the principal sources of bacteremia and generalized infectional complications of burn victims (5), and it creates the preconditions for superinfection by Gram-negative microflora, which worsens the prognosis of burn victims even more (1,3,4).

Today we can fight staphylococcus infection successfully in many cases with the help of modern therapeutic methods, including application of new antibiotics characterized by a broad spectrum and specific action. However, when complications arise from antibiotic therapy or unusual stability of staphylococcus to antibiotics is observed on the background of dramatic inhibition of immunological reactivity, staphylococcus sepsis may develop in the patients (2,10).

It is for this reason that much attention has been devoted in recent years to developing immunological methods for influencing staphylococcus infection and its toxins (6-9,11).

Beginning in 1973 the All-Union Burn Center of the Institute of Surgery imeni A. V. Vishnevskiy started employing intravenous transfusion of hyperimmune antistaphylococcus plasma (ASP) to treat severe burn trauma. ASP therapy was used on 46 patients (37 men and nine women). Most of the patients were from

21 to 50 years old. The total burn area was from 30 to 70 percent of body surface area for 42 of the patients, and from 15 to 29 percent for four patients. The severity of thermic trauma was determined not only from the extent of burns but also the extent of deep burns and the combination of burns on the body surface and burns in the respiratory tract. For 10 patients the area of deep burns was from 3 to 19 percent of body surface area, eight of these patients exhibiting burns of the respiratory tract. Sixteen patients had deep burns with an area of 20-29 percent of body surface area, and 10 of them exhibited injury to the respiratory tract. Twelve patients received deep burns with an area from 30 to 39 percent of body surface area, eight of whom suffered burns of the respiratory tract. Deep burns covered from 40 to 50 percent of body surface area in eight patients, four of whom also suffered burns of the respiratory tract.

It should be noted that all patients underwent integrated burn therapy prior to and during the period of ASP immunotherapy. Transfusions of blood, plasma, protein and synthetic blood substitutes, 10 percent glucose solution plus insulin, electrolyte solution, and novocaine were performed from three to five times a week. Some patients underwent 7-10-day courses of parenteral nutrition (daily intravenous injection of intralipids, aminazole, and 10 percent glucose solution). All patients received antibiotics (kanamycin, monomycin, gentamycin, semisynthetic penicillins), as well as cardiovascular and antihistamine preparations, prednisolone, and anabolic hormones. Vishnevskiy's ointment, boric acid, and Furacillin ointment, synthomycin emulsion, and a solution of (sul'famon), furagin, and nitrofurazone were used for local treatment of burns. Accessible additional purulent foci were revealed and drained prior to ASP therapy or during it. To heighten immunity, not less than 10 doses of ordinary γ -globulin were injected intramuscularly into almost all patients. ASP therapy was started when integrated therapy would not curtail severe staphylococcus infection.

To add greater detail to the diagnosis and assess the effectiveness of the therapy, all patients were subjected to repeated (with an interval of 1-3 days) bacteriological examinations of blood and wound exudate. The results of these examinations showed that staphylococcus was isolated from the burn surface of all patients, usually in association with Gram-negative bacilli. Staphylococcus was not isolated from wounds in pure culture until 1-3 days after burn trauma occurred. Later associations of staphylococcus with *Bacillus pyocyaneus*, *E. coli*, and *Proteus* were isolated from the wounds of all observed patients. Microflora isolated from burn wounds and blood of the patients exhibited high resistance to antibiotics. Antistaphylococcus plasma was prescribed for patients whose blood revealed staphylococcus, pathogenic or nonpathogenic, in pure culture.

Before and during therapy and immediately after the ASP therapy course we determined the blood serum concentration of staphylococcus α -antitoxin by the hemolytic method and the cell immunity indices on the basis of the extent of completion of the phagocytic process in all patients. For the purposes of control we analyzed the indices of neutrophil phagocytic function in peripheral blood of 50 healthy persons (donors). The leukocyte phagocytic activity (LPA) of these persons was 63.3 ± 2.3 percent, and the index of the extent of completion of phagocytosis (ICP) was 70.6 ± 1.7 percent.

ASP with a staphylococcus α -antitoxin titer greater than 6 antitoxin units per milliliter was transfused dropwise at a dose from 200 to 250 ml intravenously into the patients. From three to five transfusions were performed during the course of therapy with an interval of 1-4 days (predominantly with an interval of 2-3 days).

The effectiveness of this immunotherapy was evaluated from the general condition of the patients, body temperature, clinical manifestations of toxemia and infection, the course of the wound process, and data from bacteriological, hematological, and immunological analyses before and after ASP injection. Moreover the mortality of a group of patients who suffered thermic trauma of similar severity but who had not received ASP was analyzed.

Patients receiving ASP could be subdivided into groups depending on the severity of staphylococcus infection.

Group 1 contained seven patients with burns of the upper half of the torso, neck, face, and upper limbs with a total area from 15 to 43 percent of body surface area, and deep burns covering not more than 20 percent of body surface area. All of these patients exhibited burns of the respiratory tract leading to development of early pneumonia and a significantly aggravated course of burn disease. Despite integrated therapy using antibiotics with a broad spectrum of action, the overall condition of the patients remained serious. Body temperature was above 38°C. Pronounced inflammatory changes persisted in the lungs. Phenomena of general intoxication increased. All patients exhibited an unfavorable course of burn trauma and significant suppuration coupled with perifocal inflammation. The wounds epithelialized poorly. Granulations were low, pale, and hemorrhagic. Four of the patients in this group exhibited transitory staphylococcus bacteremia. Neutrophil phagocytic function was significantly inhibited among all patients.

In view of the insufficient effectiveness of this therapy and a decline in immunological indices, it was decided to subject patients in group 1 to a course of ASP therapy. At the corresponding therapy the condition of all patients improved, temperature returned to normal, and phenomena of general intoxication decreased. Analysis of blood from patients in group 1 immediately after termination of the course of ASP therapy revealed a decline in leukocyte count and a decrease in the shift of the leukocyte formula to the left. The number of leukocytes in peripheral blood increased, indicating activation of the lymphatic system.

The LPA index doubled (61.8 \pm 3.2 percent). It should be noted that following ASP therapy inflammatory changes in the lungs and in the vicinity of burns decreased for all patients in group 1. Granulation of wounds improved, making dermoautoplasty successful. Staphylococcus was not revealed in repeated blood cultures in any of the patients of this group following ASP therapy. All patients recovered, and they were released from the clinic in satisfactory condition.

Thus in relation to patients with deep burns on the body surface of relatively small area and burns of the respiratory tract complicated by severe staphylococcus infection, ASP therapy increased immunological reactivity and curtailed the infection process within a short time.

Group 2 contained 30 persons subjected to ASP therapy. For 27 of them the area of deep burns was from 20 to 50 percent of body surface area. The area of deep burns on three patients was from 15 to 19 percent of body surface area. The deep burns of these patients combined with general electrical trauma and multiple body contusions; it was for this reason that burn disease was especially severe. Sixteen out of 30 patients in this group had burns of the respiratory tract; the rest of the patients exhibited more or less widespread inflammatory burns in the lungs, which developed as a complication of severe burn disease. All patients in group 2 had high body temperature (up to 40°C). During the day the body temperature of most of them varied 2-3°C. All patients in this group exhibited phenomena of increasing general intoxication, including changes on the part of the central nervous system--inhibition, sleep disturbance, and hallucinations, while eight patients revealed intoxication psychoses. Early development of burn trauma coupled with typical hypoproteinemia and dysproteinemia was noted among all patients.

Analysis of blood from patients in group 2 revealed leukocytosis coupled with a pronounced neutrophil shift to the left as far as myelocytes, a decline in lymphocyte count, and a dramatic decrease in neutrophil phagocytic function (35.8 ± 1.4 percent).

Suppuration, accumulation of pus beneath scabs, and inflammatory infiltration of tissues about burns were noted in the burn areas of patients in this group. When patients reached the burn center after detachment of the burn scab, poorly granulated wounds remained in the burn areas with undermined margins and profuse suppuration. Four patients in group 2 exhibited profuse suppuration from wounds, deepening of the wounds, and detachment and suppurative disintegration of skin transplanted earlier 2-7 months following injury. Plasmocoagulational staphylococcus was repeatedly isolated from the blood of 17 patients in group 2. The clinical pattern of septic intoxication combined with stable bacteremia indicated that staphylococcus sepsis was developing in 16 patients of this group. Thirteen patients had additional purulent foci: Purulent chondritis of the outer ears, injection abscesses, purulent pleuritis, purulent arthritis, and abscesses in the vicinity of bedsores.

ASP was included in integrated therapy by our method for most patients in this group in the first 2-4 weeks following burn injury, and later for nine patients.

Despite the fact that the course of ASP therapy lasted only 8-12 days, immediately after treatment the patients exhibited a noticeable improvement in the way they felt and in general condition, and a decline in body temperature. Inflammatory changes in the lungs were resolved favorably. Phenomena of general intoxication decreased. Appetite improved. Dyspeptic phenomena

disappeared or decreased significantly. Protein concentration in blood serum increased, and protein fraction composition improved. Leukocytosis and the index of the shift of the leukocyte formula to the left decreased, and the number of leukocytes in peripheral blood increased. ASP transfusion elicited activation of phagocytosis in all patients (54.7 ± 2.6 percent).

After injection of ASP with titers of 6-10 antitoxin units per milliliter the level of staphylococcus α -antitoxin in the blood of patients increased to 1-2 antitoxin units per milliliter.

An increase in cellular and humoral factors of immunity made it possible to prevent development of staphylococcus bacteremia in 13 patients. Among 17 patients with stable staphylococcus bacteremia, following ASP therapy only three exhibited transitory bacteremia elicited by nonpathogenic staphylococcus. Suppuration decreased in burn areas, marginal and insular epithelialization appeared, and wound granulation improved. Dermoautoplasty was performed successfully on the background of immunotherapy, causing the results of immunotherapy to persist. Immunotherapy conducted within the first 2-4 weeks following injury was found to be especially effective. Here is an example.

Patient Z., 35 years old, was brought to the burn center on 4 October 1975 with IIIb-IV degree burns covering an area of about 50 percent of body surface area. Burn disease proceeded with phenomena of very severe general intoxication. Body temperature attained 40°C . Sleep disturbance, irritation, weepiness, and hallucinations were noted. Nine days after injury aphthous-ulcerous stomatitis developed, nausea appeared, vomit was of the consistency of "coffee grounds," and distention of the abdomen was observed. Burn disease was complicated by bilateral pneumonia. The burn scab, beneath which there was an accumulation of pus, began to undergo detachment on 30 October. Pathogenic staphylococcus was revealed in wound exudate and blood. Blood analysis on 29 October revealed: Leukocyte count--11,000, (yu.)--1.5 percent, (p.)--38 percent, (s.)--44 percent, myelocytes--1.5 percent, lymphocytes--12 percent, monocytes--3 percent. Serum protein--5.6 gm-percent; albumin--39.5 percent; globulins: α_1 --13.2 percent, α_2 --15.8 percent, β --13.2 percent, γ --18.4 percent. Immunological analysis data: LPA--34 percent; ICP--31 percent; staphylococcus α -antitoxin titer--0.5 antitoxin units per milliliter.

The patient was subjected to ASP transfusion from 31 October to 11 November. In all, 800 ml of ASP were transfused. On the background of immunotherapy the patient was subjected to stage-by-stage necrectomy and transplantation of cracked and perforated fragments of skin. All transplants took. The patient's overall condition improved. Temperature decreased to 38.5°C and lower. Blood analysis on 14 November revealed: Leukocytes--10,800, (e.)--1.5 percent, (yu.)--0.5 percent, (p.)--24 percent, (s.)--52 percent, lymphocytes--17 percent, monocytes--5 percent. Serum protein--7 gm-percent; albumins--55.7 percent; globulins: α_1 --3.5 percent, α_2 --11.1 percent, β --11.1 percent, γ --18.5 percent; the LPA was 65 percent, and the ICP was 79.5 percent. Later the patient was subjected to another three dermoautoplasty operations.

On 16 February 1976 he was released from the burn center with healed wounds in satisfactory condition.

Considering that it was possible to heighten the infection resistance of the body with ASP transfusions, even among septic patients suffering severe thermic trauma, we made an attempt to treat nine patients with burns covering from 35 to 70 percent of body surface area (group 3) complicated by staphylococcus septicopyemia. Seven patients in this group were brought to the burn center from other therapeutic institutions due to especially severe general condition, pronounced emaciation, bedsores, multiple pyemic foci in subcutaneous cellular tissue, and purulent thrombophlebitis and periphlebitis in areas of prolonged catheterization of veins. Broadening of the limits of necrotic tissue changes coupled with their purulent disintegration and profuse suppuration was observed in burn areas and in additional purulent foci. Changes in the blood indices of these patients were approximately the same as for patients in group 2, though an even greater decline of neutrophil phagocytic function was observed: LPA-- 37.5 ± 2.2 percent, ICP-- 30.7 ± 1.5 percent. Only five patients in this group were subjected to four ASP transfusions. The rest of the patients died due to septicopyemia. Out of five patients receiving four ASP transfusions, three exhibited short-term improvement of general condition. Later, however, phenomena of septic intoxication once again increased, and new pyemic foci were revealed, including in internal organs. Absence of a pronounced effect from immunotherapy in patients of this group could have been the result of the fact that the body's infection resistance could not be stimulated. In particular the indices of neutrophil phagocytic function continued to decline: LPA--down to 24.0 ± 3.9 percent, ICP--down to 20.0 ± 4.2 percent. The other patients did not reveal such a low capability for completion of phagocytosis following ASP therapy.

Comparative analysis of the results of treating patients in group 2 subjected to ASP immunotherapy and patients with burns of similar severity who had not been subjected to ASP immunotherapy showed that mortality due to infection complications was decreased by more than twice among patients treated with ASP (mortality in the group of burn victims receiving ASP was 22.9 percent, while that in the group of burn victims not receiving ASP was 51.4 percent).

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UDC 617.713-001.17-06-022.7-084-085

INFECTIOUS COMPLICATIONS OF CORNEAL CHEMICAL BURNS, THEIR TREATMENT AND PREVENTION

Odessa OFTAL'MOLOGICHESKIY ZHURNAL in Russian No 2, 1978 pp 100-104

[Article by Cand Med Sci V. M. Nepomyashchaya, Odessa Scientific Research Institute of Eye Diseases and Tissue Therapy imeni Academician V. P. Filatov]

[Text] Analysis of clinical observations made at the Institute imeni Academician V. P. Filatov in the last 10 years has shown that chemical burns are typical of most patients with recent burns receiving hospital therapy--68-78.9 percent.

Chemical burns are dominated by alkali burns (72.6 percent), acid burns making up 13.2 percent according to our data; thermochemical burns (by hot bases, due to explosion of carbide in which an alkali agent is combined with flames, and so on) make up 9.0 percent. Other chemical compounds (alcohol, chlorine, toxic chemicals, and so on) make up the smallest group of burns (5.2 percent).

Lime burns have an important place among alkali burns of the eyes (62.9 percent of all alkali burns). The number of burns caused by ammonium has increased in agriculture and industry in recent years; they are now in second place among alkali burns.

Depending on the concentration of the injurious substance, the moment at which first aid is rendered (that is, the time of action of the substance upon the eyes), and the temperature and pressure at which the substance entered the eyes, many chemical compounds can elicit both severe and especially severe eye injuries, and rather mild injuries.

Burns of the greatest severity are noted in response to concentrated acids and bases, when chemical compounds enter the eyes at the time of an explosion or under high pressure (for example industrial burns by lime and ammonia), when first aid is rendered late, and in the presence of thermochemical burns.

Thus the initial severity of injury is associated first of all with the characteristics of the chemical agent and the time of its action in the eyes; it is the principal factor influencing the subsequent course and outcome of eye burns. However, secondary infection can also play a significant role in

development of the pathological process and formation of its complications, since burnt tissues are a favorable environment for development of microorganisms, and disturbance of natural protective barriers (the mucous membrane of the eye, the epithelium and endothelium of the cornea, and so on) promotes acceleration of intoxication processes in the focus of injury, arising in response to the activity of microorganisms and necrotic decomposition of tissues.

Our analysis of microflora on 234 eyes of 173 patients with chemical burns of varying degrees of severity showed that intense antibacterial therapy does not insure sterility of the conjunctival cavity of many patients with eye burns. Upon admission, cultures were found to be sterile only for 48 eyes out of 234 (20.5 percent), usually on eyes with mild and moderate burns (it should be noted that patients were admitted to the institute at various times, from the second day to several months after injury, predominantly after unsuccessful treatment in other hospitals). As the severity of burns increased, the quantity of the most virulent microflora increased. Thus staphylococcus dominated in all severity groups among the isolated microflora (77.9 percent); however while nonhemolytic staphylococcus or *Bacillus xerosa* were usually isolated in the presence of mild burns, highly virulent microorganisms were often detected in the presence of especially severe and severe burns.

Mild burns proceeded without complications irrespective of the presence and virulence of microflora in the conjunctival sac. Corneal infiltrates yielding well to conservative therapy were noted in four cases out of 16 eyes suffering moderately severe burns from which staphylococcus was isolated. In the presence of severe burns purulent corneal infiltrates were noted in 20 eyes out of 53 (37.7 percent) from which staphylococcus was isolated, and in two cases out of 17 (11.8 percent) producing sterile cultures.

The most unfavorable course was typical of especially severe burns, in the presence of which infection was aggravated by decomposition of the cornea, and necrotic alteration of the conjunctiva elicited by burn trauma promoted development of highly severe complications such as extensive infiltrates, fusion, thinning and perforation of the cornea, exudate in the anterior chamber and so on. These complications were noted in 67 out of 82 eyes (81.7 percent) for which microflora were cultured.

In addition to having an effect on the burn process, presence of microflora also affected the results of keratoplasty performed for tectonic and therapeutic purposes on burnt eyes. Purulent infiltration of corneal tissue occurring in the transplant hinders good adaptation and requires numerous repeat operations. This is why treatment of such patients necessitated a combination of surgery with specific antibacterial therapy and immunotherapy.

Numerous studies (1-4,6,8-10,etc.) indicate that secondary infection plays a significant role in development of the pathological process of eye injuries and burns.

Kulakova's statement (5) that presence of microorganisms in exudate from the conjunctival sac does not aggravate the course of the burn process disagrees with these works. The author should have provided greater detail concerning her conclusion, since otherwise she could disorient the physician in his fight against infection accompanying burns.

Preventive measures and control of infectious complications must be performed actively from the first days following injury, no matter what the severity of the burns.

However, the possibilities for antibacterial therapy of infectious complications of eye burns are limited by the high resistance of microorganisms and their swift adaptation to new active antibacterial preparations.

We had noted earlier that highly pathogenic flora was usually found to be resistant to antibiotics. Thus staphylococcus, which has pronounced hemolytical properties, was found to be sensitive to erythromycin and streptomycin in only 14.81 percent of the cases, to penicillin in 11.11 percent of the cases, to levomycetin in 3.70 percent of the cases, and monomycin in 62.96 percent of the cases. Nonhemolytic staphylococcus exhibited sensitivity to monomycin in 100 percent of the cases, to erythromycin in 78.42 percent of the cases, to penicillin in 64.28 percent of the cases, to streptomycin in 42.85 percent of the cases, and to levomycetin in 28.53 percent of the cases.

Antistaphylococcus preparations have been used successfully in recent years to treat staphylococcus infections in pediatrics, in burn surgery, and in ophthalmology (11,14,15,etc.). Malanova et al. (7) used placental anti-staphylococcus γ -globulin against creeping ulcers of the cornea. Proskurov (12) and Protopopov (13) used staphylococcus bacteriophage against purulent eye diseases.

Pozdnyakov, Savko, and I (2) used hyperimmune antistaphylococcus plasma in integration with treatment of eye burns and their complications.*

This report presents the results of treating 26 patients with purulent corneal infiltrates, for whom the therapeutic measures included antistaphylococcus plasma; the results of preventive use of antistaphylococcus plasma on 23 eyes suffering moderately severe burns and on 37 eyes with severe burns were analyzed.

Antistaphylococcus plasma containing nine and more antitoxin units per milliliter was injected into the conjunctiva of the burnt eye at a dose of 0.5-1.0 ml, daily or every other day, with a total of 4 to 15 injections in the course; the plasma was injected together with a 2 percent novocaine solution to reduce pain.

*Efficiency proposal No 288, 14 March 1973.

Absorption of corneal infiltrates, acceleration of epithelialization, elimination of the inflammatory reaction, and improvement of vision were the indices of successful treatment.

Out of 29 patients with corneal infiltrates, most of them were admitted a long time after injury--from 6-8 days to several months; only three of the patients were admitted 2-3 days after injury. Upon admission, staphylococcus was detected on 18 eyes (69.2 percent), yeast-like fungi were noted on one, cultures were negative in five cases, and cultures were not taken from two eyes. Prior to admission to the hospital the patients had taken various antibacterial preparations unsuccessfully.

It should be noted that negative cultures in the presence of corneal infiltrates did not fully exclude the possibility that the latter were infectious, since these patients were undergoing antibacterial therapy at the moment of admission to the institute, leading to sanitation of the conjunctival cavity but not having a significant influence on the process occurring in the cornea.

Inclusion of immune antistaphylococcus plasma into integrated therapy of patients with purulent corneal infiltrates was found to be highly effective. Absorption of corneal infiltrate, subsidence of the inflammatory phenomena, and corneal epithelialization were noted among all 26 patients. Growth in corneal transparency resulted in an increase in visual acuity of 22 eyes. The highest visual acuity figures (0.5-1.0) were obtained for all patients with moderately severe burns (eight eyes). Clouding of the cornea to one extent or another was noted among patients with severe burns (18 eyes) upon release, and visual acuity did not exceed 0.3-0.4 (Table 1).

Table 1. Visual Acuity Dynamics Accompanying Treatment of Purulent Corneal Infiltrate by Antistaphylococcus Plasma.

| (1) Острота зрения до лечения | (2) Общее коли- чество глаз | (3) Острота зрения после лечения | | | | | | | |
|-------------------------------------|-----------------------------------|----------------------------------|-------------|-----------|-----------|----------|----------|----------|---------|
| | | 1 pr. in- certa | 1 pr. certa | 0,01-0,02 | 0,03-0,05 | 0,06-0,1 | 0,12-0,2 | 0,25-0,5 | 0,5-1,0 |
| $\frac{1}{8}$ pr. incerta | 1 | 1 | | | | | | | |
| $\frac{1}{8}$ pr. certa | 8 | | 2 | 1 | 3 | 1 | 1 | | |
| 0,01-0,02 | 7 | | | 1 | 1 | — | 3 | 1 | 1 |
| 0,03-0,05 | 5 | | | | | | 1 | 3 | 1 |
| 0,06-0,1 | 4 | | | | | | | 2 | 2 |
| 0,12-0,2 | 1 | | | | | | | | 1 |
| (4) Всего | 26 | 1 | 2 | 2 | 4 | 1 | 5 | 6 | 5 |

Key:

- | | |
|-----------------------------------|--------------------------------|
| 1. Visual acuity prior to therapy | 3. Visual acuity after therapy |
| 2. Total number of eyes | 4. Total |

Antistaphylococcus plasma was used in conjunction with eye burn therapy for preventive purposes in the early period of burn injury on 75 eyes suffering severe and moderately severe burns. The group analyzed included patients with uncomplicated burns who had been admitted not more than 1-4 days following injury.

Microbiological analyses were conducted on 55 out of 75 eyes. Staphylococcus was isolated in 35 cases, Streptococcus was isolated from one eye, bacilli were isolated from five, and yeast-like fungi were isolated from two. Cultures from 12 eyes were sterile.

An analysis of the clinical observations showed that the therapy we performed prevents development of infectious complications such as corneal infiltrates and ulcers, which were not noted in any case of early immunotherapy, that it stimulates regenerative processes in the cornea, and that it promotes resorption of clouding substances and a rise in visual acuity.

In the overwhelming majority of cases of moderately severe burns visual acuity increased considerably following therapy (Table 2).

Table 2. Results of Treating Patients With Moderately Severe Burns.

| Острота зрения до лечения (1) | Общее количество глаз (2) | (3) Острота зрения после лечения | | | | | |
|----------------------------------|------------------------------|----------------------------------|-----------|----------|----------|----------|---------|
| | | 0,01—0,02 | 0,03—0,05 | 0,06—0,1 | 0,12—0,2 | 0,25—0,5 | 0,6—1,0 |
| 0,01—0,02 | 5 | — | — | — | — | 2 | 3 |
| 0,03—0,05 | 3 | — | — | — | — | — | 3 |
| 0,06—0,1 | 8 | — | — | 1 | — | 1 | 6 |
| 0,12—0,2 | 5 | — | — | — | — | 1 | 4 |
| 0,25—0,5 | 7 | — | — | — | — | 1 | 6 |
| (4) Всего | 28 | | | 1 | | 5 | 22 |

Key:

1. Visual acuity prior to therapy
2. Total number of eyes
3. Visual acuity after therapy
4. Total

The results were also favorable in the group of patients with severe burns. Despite severe damage to the cornea improvement in visual acuity was noted for 35 eyes (74.46 percent), the improvement being significant for 22 eyes. Pronounced scarring on four eyes led to a decline in vision, and visual acuity of eight eyes did not change (Table 3).

Summarizing the research, it should be concluded that the unique features of severe eye burns created favorable conditions for development of microflora in the burnt eye and formation of infectious complications. In this case the frequency of these complications is directly dependent on the severity

Table 3. Results of Treating Severe Eye Burns.

| (1) Острота зрения до лечения | (2) Общее коли- чество глаз | (3) Острота зрения после лечения | | | | | |
|-------------------------------------|-----------------------------------|----------------------------------|-----------|-----------|----------|----------|----------|
| | | pr. certa 1/8 | 0,01-0,02 | 0,03-0,05 | 0,06-0,1 | 0,12-0,2 | 0,25-0,7 |
| 1/8 pr. certa | 18 | 3 | 7 | 4 | 1 | | 3 |
| 0,01-0,02 | 14 | 1 | 4 | 2 | 1 | 3 | 3 |
| 0,03-0,05 | 5 | 1 | | 1 | 2 | | 1 |
| 0,06-0,1 | 5 | | 2 | | | | 3 |
| 0,12-0,2 | 5 | | | | | | 5 |
| (4) Всего | 47 | 5 | 13 | 7 | 4 | 3 | 15 |

Key:

- | | |
|-----------------------------------|--------------------------------|
| 1. Visual acuity prior to therapy | 3. Visual acuity after therapy |
| 2. Total number of eyes | 4. Total |

of burn injury, the depth of necrotic tissue injury, loss of physiological barriers, and trophic disturbances elicited by the burn.

Specific antibacterial therapy of eye burns must begin in the first days following injury by prescription of antibacterial preparations of a broad spectrum of action coupled with periodic control for the presence of microflora and the taking of an antibioticogram which should predetermine prescription of antibacterial preparations in each concrete case.

The effectiveness of antibacterial therapy is significantly increased by inclusion, in the complex of therapeutic measures, of antistaphylococcus plasma and γ -globulin, which have the valuable property of pronounced influence upon the pathological process caused by stable species of microflora, which are usually the ones causing complications in the presence of eye burns.

Clinical observations show that early application of specific immunotherapy in many cases prevents purulent complications of eye burns in the presence of pathogenic staphylococcus.

Immune antistaphylococcus preparations enhance the protective properties of burnt tissues, intensify the antimicrobial action of the antibiotics employed, curtail the infectious process, promote resorption of purulent corneal infiltrates, and improve the prognosis of keratoplastic operations in the presence of burns with a complicated course.

The results of our research indicate the suitability of including subconjunctival injections of antistaphylococcus plasma in complex therapy of patients with eye burns.

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CHANGES IN RNA BIOSYNTHESIS IN CHICK LIVER IN THE PRESENCE OF COCCIDIOSIS

Leningrad PARAZITOLOGIYA in Russian No 3, 1978 pp 263-266

[Article by A. V. Zver'yanov, Yu. P. Zerov, and A. Ye. Khovanskikh, All-Union Scientific Research Institute of Bird Diseases, Leningrad]

[Text] The fractional composition and metabolic intensity of individual chick liver RNA fractions were studied in the course of experimental coccidiosis. A noticeable increase (60 percent) was noted in the metabolic intensity of information RNA in the presence of no change in its content. A significant increase was noted in the biosynthesis of rRNA precursors and, as a consequence, an increase in the content of the precursors of and mature 18 S rRNA, with no change occurring in the concentration of 28 S rRNA. The role of the observed changes in this pathological process is discussed.

A number of data indicate the important role of biosynthetic processes occurring in the liver of infected chicks in the pathogenesis of coccidiosis. It has been demonstrated that the blood serum of infected chicks exhibits a dramatic decline in albumin concentration (3). This phenomenon is probably caused by intensive hemorrhaging through ruptures in the intestinal wall observed when the parasite *Eimeria tenella* multiplies. Research in our laboratory confirms a decrease in serum albumin concentration, on the background of which a significant increase in the intensity of blood serum albumin biosynthesis was demonstrated (5). Because the liver is the source of serum albumin, there is doubtless interest in studying the liver's machinery for synthesizing proteins, RNA in particular.

The objective of this work was to study biosynthesis of the basic functional classes of RNA in the liver of chicks infected by *E. tenella*, order Coccidia.

Materials and Methods

Ten to 12 day old White Leghorn chicks (cross-288) were infected *per os* by a culture of sporulated *E. tenella* oocytes at a dose of 10,000 oocytes per chick. Chicks of the same age maintained in conditions precluding spontaneous infection served as the control.

In order to determine the intensity of total RNA biosynthesis, in different time intervals following infection we injected 100 microcuries of $\text{NaH}_2\text{P}^{32}\text{O}_4$ per 100 gm live weight intraperitoneally. One hour later the chicks were killed, and the liver RNA concentration was determined according to (6). C^{14} -orotic acid labeling (300 microcuries per 100 gm weight) was employed to study the metabolic intensity of individual RNA fractions. Total liver RNA was isolated by phenol extraction with the sample heated in the presence of sodium dodecylsulfate (7).

Information RNA (containing poly-A units) was isolated by column fractionation with our modification of the nonmodified cellulose of Schutz et al. (9); in our modification, MgCl_2 was substituted by 10^{-4} M EDTA.

Electrophoresis in 2.5 percent polyacrylamide gel (PAAG) was performed according to Loening's method (8). The stained gels were subjected to densitometry using a modified MF-4 microphotometer. To determine radioactivity, the gels were cut into disks 3 mm thick, placed in test tubes, and dried in a thermostat at 65° . The PAAG was broken down by adding 1 ml of 30 percent hydrogen peroxide to each test tube. The test tubes were allowed to stand for several hours at 65° to permit peroxide breakdown.

The radioactivity of RNA preparations was determined with a Mark-2 ("Nuclear-Chicago") scintillation counter in a dioxane scintillator (7 gm PPO, 0.25 gm POPOP, and 80 gm naphthalene per liter of dioxane).

Results and Discussion

It was demonstrated in the initial phase of the work that an increase occurred in both the concentration (by 1.4 times) and the radioactivity (by 1.8 times) of total liver RNA in infected chicks 6 days after infection. Significant changes were not observed earlier, and after 10 days both of these parameters declined to normal. On the basis of these data, we studied biosynthesis of individual RNA fractions not until 6 days following infection.

The results of dividing total liver RNA preparations into fractions containing poly-A (mRNA and its precursors) and those not containing poly-A are shown in Table 1. We can see from these data that the proportion of mRNA decreases after infection. However, if we account for the total increase in RNA concentration we find that the quantity of mRNA per unit tissue weight remains constant. At the same time the metabolic intensity of both RNA fractions increases significantly after infection.

The figure shows the results of electrophoretic separation of RNA in 2.5 percent PAAG. We can see clearly that ribosomal precursors and 18 S rRNA accumulate. For practical purposes the concentration of 28 S rRNA does not change. A significant increase in radioactivity in the zone of rRNA precursors is observed. An attempt was made to quantitatively assess the observed changes; the area of peaks on densitograms was determined for this purpose by a weighting procedure. The obtained data are shown in Table 2 together with the determinations of radioactivity of the corresponding RNA fractions.

Table 1. Fractional Composition of Total Chick Liver RNA; Cellulose Chromatography.

| Фракция РНК (1) | Условия опыта (2) | Содержание Фракции, % (3) | Удельная радиоактивность (4) расп./мин. · мг |
|--------------------------|----------------------|------------------------------|---|
| (5) Не содержащая поли-А | (7) Опыт | 95.8 (± 0.6) * | 57000 (± 1200) |
| | (8) Контроль Р | 94.2 (± 0.8) < 0.01 | 36800 (± 1400) < 0.001 |
| (6) Содержащая поли-А | (7) Опыт | 4.2 (± 0.6) | 580000 (± 22000) |
| | (8) Контроль Р | 5.8 (± 0.7) < 0.01 | 360000 (± 18000) < 0.001 |

*The 199 confidence interval is shown in parentheses.

Key:

- | | |
|--|--------------------------|
| 1. RNA fraction | 5. Not containing poly-A |
| 2. Experimental conditions | 6. Containing poly-A |
| 3. Fraction concentration, % | 7. Experiment |
| 4. Unit radioactivity, disintegrations per minute per mg | 8. Control |

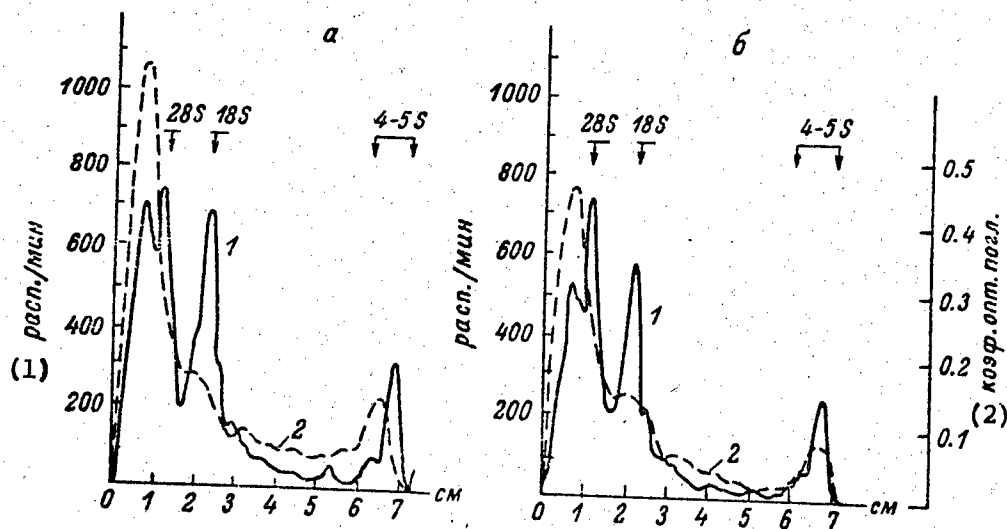
Table 2. Concentration and Radioactivity of Electrophoretic Fractions of Chick Liver Total RNA.

| Фракция РНК (1) | Условия опыта (2) | (3) Содержание РНК в усл. ед. | | (6) Радиоактивность (расп./мин.) | |
|--------------------|----------------------|-------------------------------|---|----------------------------------|---|
| | | опытные данные (4) | пересчитано на ед. веса ткани (5) | опытные данные (4) | пересчитано на ед. веса ткани (5) |
| $\geq 32S$ | (7) Опыт | 76 (± 17) * | 101 | 4700 (± 500) | 6300 |
| | (8) Контроль Р | 62 (± 16) < 0.05 | 62 | 3800 (± 400) < 0.01 | 3800 |
| 28S | Опыт | 50 (± 19) | 71 | | |
| | Контроль Р | 71 (± 13) < 0.01 | 71 | | |
| 28S+18S | Опыт | | | 3100 (± 300) | 4100 |
| | Контроль Р | | | 3600 (± 600) > 0.05 | 3600 |
| 18S | Опыт | 56 (± 9) | 79 | | |
| | Контроль Р | 45 (± 7) < 0.01 | 45 | | |
| 5S+4S | Опыт | 33 (± 10) | 49 | 1370 (± 250) | 1850 |
| | Контроль Р | 33 (± 19) > 0.05 | 33 | 660 (± 220) < 0.01 | 660 |

*The 199 confidence interval is shown in parentheses.

Key:

- | | |
|---------------------------------------|---|
| 1. RNA fraction | 5. Corrected per unit tissue weight |
| 2. Experimental conditions | 6. Radioactivity (disintegrations per minute) |
| 3. RNA concentration, arbitrary units | 7. Experiment |
| 4. Experimental data | 8. Control |



Fractional composition (curve 1) and radioactivity distribution (curve 2) following separation of total liver RNA preparations by electrophoresis in 2.5 percent PAAG: *a*--Infected chicks, *b*--healthy chicks.

Key:

1. Disintegrations per minute
2. Optical absorption coefficient

Table 2 also shows data accounting for the increase in total RNA concentration during the analyzed period of disease in order to portray the real pattern of changes occurring in liver cells. When the data are corrected in this way, we are dealing not with the proportions of individual fractions in the RNA preparation but rather with their concentrations in liver tissue. Data treated in this fashion confirm that an increase occurs in the concentration of ribosomal precursors (1.6 times) and 18 S rRNA (1.8 times). In addition an increase in the concentration of low molecular weight RNA (by 1.4 times) is revealed. The concentrations of 28 S rRNA are identical in the liver of sick and healthy chicks.

The radioactivity determinations show that radioactivity in rRNA precursors (the 32 S zone) increases significantly while their unit radioactivity remains constant. Because the time of incubation with C^{14} -orotic acid coincides with the time of exchange of rRNA nuclear precursors, these data indicate that synthesis of rRNA undergoes activation while the rate of its maturation is constant. The short labeling time is also responsible for the insignificant changes occurring in the zone of mature rRNA. The greatest change in radioactivity is observed in the zone of low molecular weight RNA (almost by three times). This most likely attests to intensification of the metabolism of certain classes of RNA, since the intermediate RNA decomposition products accumulate in this zone.

We can gain a general impression of changes in RNA biosynthesis in the presence of coccidiosis from these data. Obviously activation of rRNA precursor biosynthesis leads to selective accumulation of 18 S rRNA. Basing ourselves on the idea that both basic classes of rRNA have a common precursor (1), we can assume that a certain proportion of the precursors of 28 S rRNA break down in the nucleus in the course of maturation, which should lead to the increase in the radioactivity of RNA in the low molecular weight area we observe. Because the greater part of 18 S rRNA is produced from small ribosomal subunits, as a result of the observed changes the proportion of small presubunits in the cytoplasm of infected chick liver cells increases. Owing to this the frequency of initiation of protein synthesis and the intensity with which mRNA is used in translation increase, which agrees with the increase in mRNA metabolism we observed (Table 1). Consequently while the quantity of mRNA remains unchanged, the rate of protein synthesis experiences a dramatic increase. This hypothesis is directly confirmed by research on liver protein biosynthesis in the presence of coccidiosis (2). Thus research on RNA biosynthesis in chick liver tissue in the presence of coccidiosis helps to clarify the mechanisms of the liver's compensatory action (5), which in this case expresses itself as intensified secretion of albumin, resulting in intensification of protein biosynthesis in the liver.

Conclusions

1. The maximum increase in concentration and metabolic intensity of RNA in chick liver tissue in the presence of experimental coccidiosis elicited by *E. tenella* is observed 6 days after infection.
2. Also typical during this time are changes in the fractional composition and biosynthesis of individual RNA fractions in infected chick liver: Intensification of rRNA precursor biosynthesis, growth in the rate of mRNA metabolism, and selective accumulation of 18 S rRNA in the presence of a constant concentration of mRNA and 28 S rRNA.
3. The observed changes in RNA metabolism are apparently responsible for intensification of protein synthesis in the liver in the presence of coccidiosis.

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PATHOLOGY

UDC 615.917'412.212.036.11-057:616.8-091-07

MORPHOLOGICAL CHANGES IN THE NERVOUS SYSTEM IN ACUTE PERORAL POISONING WITH DICHLOROETHANE

Moscow ARKHIV PATOLOGII in Russian No 5, 1978 pp 49-53

[Article by G.A. Akimov and I.P. Kolesnichenko, Leningrad, Department of Neural Diseases (chief--Professor G.A. Akimov) of the Military Medical Academy imeni S.M. Kirov, City Emergency Hospital No 10 (chief physician--V.S. Zinov'yev)]

[Text] A morphological study was made of the nervous system of 14 patients who had died of acute peroral poisoning with dichloroethane. Considerable vascular disorders (perivascular edema, congestive plethora, vascular dystony and small-focal hemorrhages) and diffuse changes in the brain cells were revealed. The main forms of parenchymatous changes in the brain and spinal cord were acute swelling, shriveling, severe disease and ischemic changes in the nerve cells, which occurred 3-6 hours after taking the dichloroethane. The pathomorphology of the fibers of the spinal cord and peripheral nerves was manifested by a moderately marked myelin degeneration.

ARKH. PAT., No 5, 1978, p 49. Illustrations--3; Bibliography--9 entries.

Key words: brain, spinal cord, peripheral nerves, dichloroethane.

Acute peroral poisonings with dichloroethane have been described by many authors, and they are distinguished by the extreme severity of the course and frequently have a fatal outcome even when a negligible amount of the toxic substance is taken (A.A. Yaroslavskiy; T.V. Novikovskaya; M.V. Natsyuk and A.D. Mudritskiy; Martin and coauthors; Schonborn and coauthors).

The works devoted to the study of the morphological changes in the nervous system in acute peroral poisoning with dichloroethane are few in number and have been done mainly by domestic authors (P.P. Dvizhkov; S.D. Dusheyko;

M.S. Tolgskaya). They note considerable vascular disorders and less marked changes in the brain cells. In the accessible literature no works could be found devoted to a study of the morphological changes in the spinal cord and peripheral nerves. The information on the nature of the morphological changes in the nervous system, depending on the period of occurrence of the fatal outcome, is quite inconsistent. The small amount and contradictory nature of the literary data made it necessary to study the nature of the morphological changes in the nervous system in acute dichloroethane poisoning at various periods from the moment of the poisoning up to the fatal outcome--after 3-6, 14-17 hours and 1 and 7 days.

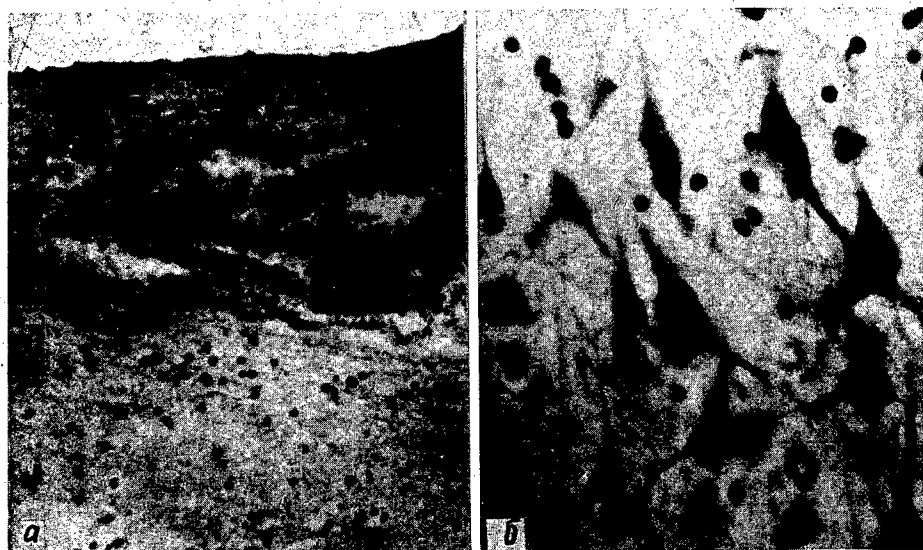


Figure 1. Vascular Disorders of the Brain and Changes in the Cells of the Cortex of the Large Hemispheres in Acute Dichloroethane Poisoning

a--subependymal hemorrhage. Pons varolii. Van Gieson's stain. X 112.5;
b--acute swelling of nerve cells of 2d and 3d layers of the cortex with some cells passing into a state of "severe disease." Posterior central gyrus at the right. Nissl's stain. X 300.

A histological study was made of the nervous system of 14 patients who had died from acute peroral poisoning with dichloroethane. The fatal outcome occurred in 4 patients 3-6 hours after the dichloroethane had been taken, in 4--after 14-17 hours, in 5--after 1 day, and in 1--after 7 days. The amount of dichloroethane taken, according to anamnestic data, varied from 30.0 to 150.0.

The pathomorphological study was made using B.S. Doynikov's method, which specifies a histological study of the main divisions of the central and peripheral nervous system (G.A. Akimov and V.V. Semenova-Tyan-Shanskaya).

Nissl's and Van Gieson's stains and hematoxylin-eosin were used to study the condition of the cell elements and vessels. The medullary fibers were stained by Marchi's method. The astrocytes were revealed by Cajal's method of a solution of gold chloride and mercuric chloride.

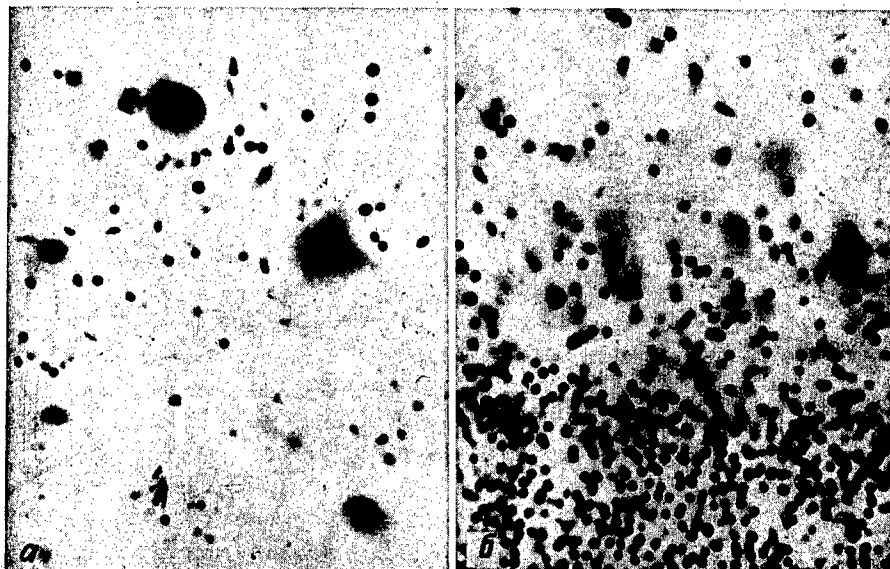


Figure 2. Pathomorphology of the Cerebellum and Subcortical Ganglia in Acute Dichloroethane Poisoning.

Nissl's stain. X 300. a--ischemic changes in the cells of the caudate nucleus at the left; b--ischemic changes in the piriform neurocytes (Purkinje's cells) of the cerebellum.

In a macroscopic study of the brain and spinal cord, attention was drawn by the plethora of the meninx vasculosi, and individual punctate hemorrhages and edema of the brain substances were detected.

In a microscopic study, vasodilation, stasis and marked perivascular edema were noted. In those who had died 3-6 hours and 1 day from the moment of the poisoning, along with the dilated vessels, in various divisions of the brain, collapsed vessels were detected, which gave evidence of their dystonic changes. In the hemispheres, large ganglia of the base and stem of the brain, small focal hemorrhages were revealed, primarily localized in the brain stem and subcortical formations (Fig. 1, a). The main type of pathological changes in the nerve cells of the cerebral cortex was acute swelling with a pattern of marked chromatolysis (Fig. 1, b). The greatest changes were discovered in the cells of the 2d-4th layers of the cortex. Nerve cells were revealed in a condition of "severe disease," as well as "shadow cells," which were most often detected one day after the ingestion of the toxic

substance. Shriveled nerve cells and cells with hydropic changes were less frequently encountered. The ischemic changes in the nerve cells of the cortex, in the overwhelming majority of the cases, were revealed 1 day after and less often--14-17 and 3-6 hours after the poisoning.

Among the characteristic changes in the cells of the large ganglia of the base and hypothalamic area were acute swelling with symptoms of chromatolysis. Nerve cells with "severe" ischemic changes were revealed. There were considerably more of them among the patients who had died 1 day after taking the dichloroethane (Fig. 2, a), and cells with symptoms of neuronophagia were also found in these same patients. Similar changes were also detected in the cerebellum. Most of the piriform neurocytes of the cerebellum were found in a condition of acute swelling with symptoms of chromatolysis. "Serious" changes in the piriform neurocytes and the dentate nucleus were often detected. Cells were detected with ischemic changes and focal prolapses of the piriform neurocytes, with the preservation of the molecular and granular layers of the cerebellar cortex (Fig. 2, b). These changes were more pronounced among the patients who had died one day after the poisoning. The changes in the brain stem cells were represented by a pattern of acute swelling with signs of chromatolysis and the presence of "serious" changes in the nerve cells. The number of cells with serious changes considerably predominated among the patients who had died one day after taking the dichloroethane. The serious changes were most often encountered in the cells of the superior olivae, and nuclei proper of the pons, and less often--in the cells of the nuclei of the craniocerebral nerves. Shriveled nerve cells were often detected. These changes were most often noted in the cells of the motor nuclei of the vagus and hypoglossal nerves among patients who had died 3-6 hours after poisoning.

The most characteristic types of pathological changes in the cells of the spinal cord were acute swelling and shriveling. The cells of the anterior horns changed more strongly than the cells of the lateral and posterior horns. In patients who had died 3-6 hours after poisoning, shriveled nerve cells were mainly detected (Fig. 3, a). Among patients who had died 14-17 hours and 1 day after taking the dichloroethane, the nerve cells were most often revealed to be in a state of acute swelling with marked chromatolysis and transition to "serious cell disease." Quite considerable sections of rarefaction and prolapse of the cells of the anterior, lateral and posterior horns of the spinal cord were often revealed. Similar changes were also detected in the intervertebral ganglia. In the patient who had died 7 days after taking the dichloroethane, there was a predominance of symptoms of acute swelling of the nerve cells, and "serious" cell changes were found less often than in the preceding observations. No nerve cells with ischemic changes were detected.

The changes in the nerve fibers of the spinal cord and peripheral nerves were represented by a pattern of swelling and moderately marked myelin degeneration with the formation of small granules (Fig. 3, b). The changes in the macroglia were of a dual nature. In the patients who had died from

3-6 hours after the poisoning, the changes were expressed in hypertrophy of the astrocytes, swelling and ectopia of the nuclei. Among those who had died 1 day after the poisoning, the pattern of changes in the astrocytes was mainly regressive in nature. The astrocytes had shriveled and the nucleus diminished in size and took on a dark coloring, and the body of the cell became narrow and pyknomorphous. Dystrophic changes in the astrocytes could be observed in several preparations. The changes in the oligodendrogliae were manifested by a proliferation of the drainage cells, with the formation of individual multicellular complexes or series.

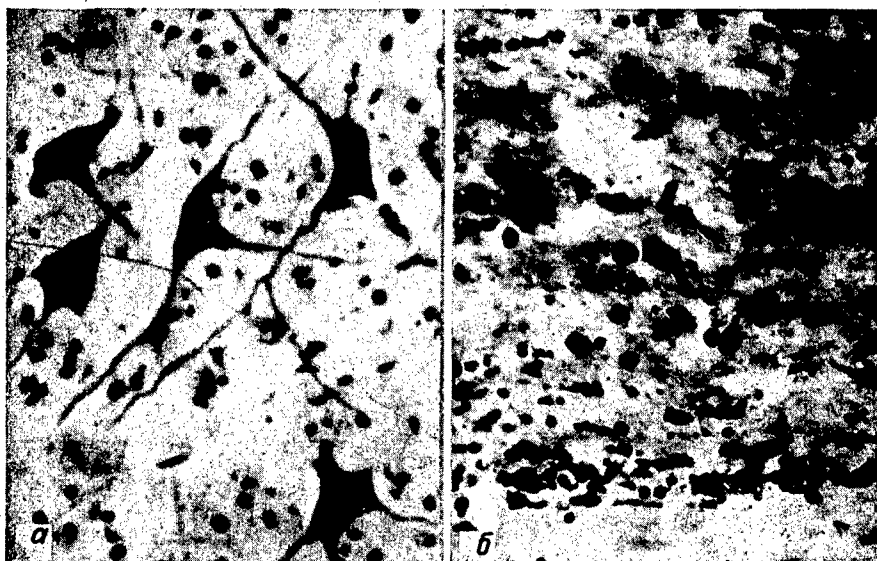


Figure 3. Morphological Changes in the Spinal Cord in Acute Dichloroethane Poisoning.

a--shriveling of the nerve cells of the anterior horns of the thoracic section of the spinal cord. Nissl's stain. X 112.5; b--degeneration of the medullary fibers of the thoracic section of the spinal cord. Marqui's stain. X 112.5.

An analysis of the studies made shows that as the result of the direct toxic action of the dichloroethane on the somatic and vegetative nervous system, a disturbance in the neuroendocrinal regulation of the vascular tonus and increased penetrability of the vascular walls, as well as viscerogenic effects caused by damage to the liver and kidneys, widespread serious, primarily dystrophic, changes occur in the cells of the brain and the spinal cord.

Conclusions

1. In acute peroral poisoning with dichloroethane, widespread morphological changes are observed in the nervous system, caused mainly by the direct action of the toxic substance.

2. The principal manifestations of vascular disorders of the brain are perivascular edema, congestive plethora, a disturbance in the tonus of the vessels and their increased penetrability and small focal hemorrhages. Among the characteristic forms of parenchymatous changes in the brain and spinal cord are acute disease (swelling), "serious disease," shriveling and ischemic changes in the nerve cells.

3. The vascular and parenchymatous changes predominate in the brain stem, hypothalamic area and large ganglia of the base. They appear 3-6 hours after the poisoning and reach maximum development with respect to the degree of markedness and distribution after 17-24 hours.

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PHARMACOLOGY

UDC 615.217.34.015.45:612.82

EFFECT OF BENACTYZINE AND SPASMOLYTIN ON BRAIN CIRCULATION AND OXYGEN METABOLISM

Moscow FARMAKOLOGIYA I TOKSIKOLOGIYA in Russian No 3, 1978 pp 302-306

[Article by A. I. Beketov, I. P. Fomochkin, N. A. Skoromnyy, and G. F. Kruty-porokh, School of Pharmacology, Crimean Medical Institute]

[Text] It is established in experiments with dogs that benactyzine and spasmolytin have a biphasal action on brain circulation. The difference in oxyhemoglobin concentrations in arteries and veins declines in response to benactyzine, and it increases when spasmolytin is employed. Absorption of oxygen by the brain of dogs subjected to acute intoxication by chlorophos decreases, and when spasmolytin is injected it increases.

Published information (4,5) indicates that small doses of benactyzine (0.5 mg/kg) decrease brain circulation and increase the resistance of brain vessels, while large doses (2-3 mg/kg) have a biphasal action on brain blood supply and increase local circulation. According to (13), after an insignificant decrease benactyzine causes a rise in the tone of major brain vessels, dilating pial arteries only at large concentrations ($1 \cdot 10^{-3}$ and $5 \cdot 10^{-3}$). We were unable to find data on the effect of spasmolytin on brain circulation.

The objective of our research was to comparatively study the action of benactyzine and spasmolytin on total brain circulation and oxygen absorption.

Research Methods

Blood circulation and oxygen cycling were studied in acute experiments on anesthetized dogs (30 mg/kg ethaminal sodium and 20 mg/kg thiopental sodium intraperitoneally) using an integrated method described in detail earlier (2). We recorded the volumetric blood flow rate from the confluence of brain venous sinuses, arterial pressure, respiration, oxyhemoglobin concentration (HbO_2) in arterial blood and in venous blood returning from the brain, we determined the HbO_2 difference for arterial and venous blood, and we computed brain oxygen absorption. We used heparin to prevent blood coagulation (1,500 units/kg). In experimental series I (21 dogs) benactyzine (2 mg/kg) and spasmolytin (1 mg/kg) were injected into intact animals intravenously, and

in series II (18 dogs) benactyzine and spasmolytin were injected 20 minutes after injection of chlorophos into the animals (70 mg/kg intravenously).

Results and Discussion

The data in Table 1 show that benactyzine does not cause statistically significant changes in volumetric blood flow rate and in brain oxygen absorption and tension in intact dogs. However, analysis of individual experiments showed that 5-6 minutes after injection of the preparation, when arterial pressure had not undergone significant change, the flow of blood from the confluence of brain venous sinuses increased by 2-42 percent in comparison with the initial level in 7 out of 10 experiments. Later, although blood pressure declined consistently, a tendency toward reduced circulation was noted. HbO₂ concentration in brain venous blood changed irregularly in the first 20 minutes following benactyzine injection, after which it decreased. Oxygen saturation of arterial blood and the difference in HbO₂ concentration in arterial and venous blood decreased.

As was demonstrated earlier (3), and as was seen from the present observations, acute intoxication of dogs by chlorophos was accompanied by an increase in the volumetric blood flow rate, a rise in brain oxygen absorption, and a decrease in arterial blood oxygenation and the difference in HbO₂ concentration in arteries and veins. Injection of benactyzine on this background elicited similar changes in a number of indices, as in the intact animals. Brain circulation increased by 2-24 percent in the first 10 minutes in eight out of nine experiments, declining toward the end of the observations. In eight out of nine experiments the difference in HbO₂ concentration in arteries and veins decreased by 2-50 percent, and oxygenation of arterial blood declined (see Table 1). At the same time we noted a pronounced decline in brain oxygen absorption, which was not revealed in intact animals.

Other results were obtained when spasmolytin was used on dogs subjected to acute intoxication by chlorophos. Brain circulation increased by 2-43 percent in three experiments and decreased by 2-40 percent in six as compared to the initial figures. Arterial pressure and brain oxygen tension declined, while the artery-vein HbO₂ concentration difference and brain oxygen absorption increased (see Table 2). In eight out of nine experiments oxygen saturation of arterial blood increased while changes in HbO₂ concentration in brain venous blood were irregular. Consequently in contrast to intact dogs, a significant rise in brain oxygen consumption was noted in response to spasmolytin among animals intoxicated by chlorophos. This increase was the product of improved oxygen delivery due to higher oxygenation of arterial blood, since in most cases brain circulation decreased.

Thus our data show that having a biphasal action on brain circulation (a distinct decrease in circulation is noted following a short-term increase), benactyzine and spasmolytin do not cause consistent changes in absorption of oxygen from blood in intact dogs. The difference in HbO₂ concentration in arteries and veins decreases in response to benactyzine and increases when spasmolytin is employed.

Table 1. Effect of Benactyzine (2 mg/kg) on Brain Circulation and Oxygen Absorption.

| Показатель (1) | (2) Интактные животные (11 опытов) | | | | (5) Острое отравление хлороформом (9 опытов) | | | |
|---|---|-------------------------------------|--------|----------|---|-------------------------------------|--------|---------|
| | исходные данные ($\bar{x} \pm S\bar{x}$) (3) | (4) | | | исходные данные ($\bar{x} \pm S\bar{x}$) (3) | (4) | | |
| | | 4 мин | 20 мин | 50 мин | | 4 мин | 20 мин | 50 мин |
| | | $\Delta\bar{x} \pm \Delta S\bar{x}$ | | | | $\Delta\bar{x} \pm \Delta S\bar{x}$ | | |
| (6) Объемная скорость кровотока из сто- ка венозных синусов мозга, мл/мин | 80±5 | +8±3,9 | +2±3,9 | -9±5,5 | 86±9 | +1±2 | -3±7 | -16±4* |
| (7) Поглощение кислорода мозгом, % | 100 | -9±7 | -2±7 | -5±8 | 100 | -13±5* | -13±4* | -19±12 |
| (8) Напряжение кислорода в мозге, % | 100 | +1±9 | -12±9 | -23±12 | 100 | +9±7 | -11±13 | -20±22 |
| (9) HbO ₂ артериальной крови, % | 85±1,3 | -4±0,9* | -3±1,4 | -8±2,6* | 76±2,7 | -5±2* | -5±2* | -12±3* |
| (10) HbO ₂ оттекающей от мозга венозной крови, % | 49±1,2 | +4±4 | -2±4 | -22±5* | 44±2,1 | +1±2 | -1±4 | -15±6,5 |
| (11) Артериовенозная разность по HbO ₂ , % | 36±1,3 | -13±5,5* | -1±5,8 | +11±8 | 32±4 | -12±7 | -6±10 | -4±17 |
| (12) Артериальное давление, мм рт. ст. | 99±9 | -3±2 | -7±2* | -17±3,2* | 88±9 | -1±2 | -6±3 | -27±15 |

Note: Here and in Table 2, asterisks indicates statistically significant changes
($P < 0.05$).

Key:

1. Index
2. Intact animals (11 experiments)
3. Initial data
4. Minutes
5. Acute intoxication by chlorophos (nine experiments)
6. Volumetric blood flow rate from confluence of brain venous sinuses, ml/min
7. Brain oxygen absorption, percent
8. Brain oxygen tension, percent
9. HbO₂ of arterial blood, percent
10. HbO₂ of venous blood draining from brain, percent
11. Arterial-venous HbO₂ concentration difference, percent
12. Arterial pressure, mm Hg

Table 2. Effect of Spasmolytin (1 mg/kg) on Brain Circulation and Oxygen Absorption.

| Показатель (1) | (2) Интактные животные (10 опытов) | | | (6) Острое отравление хлороформом (9 опытов) | | |
|---|---|--------------------------------|----------|---|--------------------------------|---------|
| | (3) исходные данные ($\bar{x} \pm Sx$) | (4) период введения | (5) | (3) исходные данные ($\bar{x} \pm Sx$) | (4) период введения | (5) |
| | | 30 мин | 50 мин | | 30 мин | 50 мин |
| | | $\Delta \bar{x} \pm \Delta Sx$ | | | $\Delta \bar{x} \pm \Delta Sx$ | |
| (7) Объемная скорость кровотока из сто- ка венозных синусов мозга, мл/мин | | | | | | |
| (8) Поглощение кислорода мозгом, % | 80±6 | +7±2* | -18±6,2* | 86±6 | +5±3 | -5±11 |
| (9) Напряжение кислорода в мозге, % | 100 | +1±5 | -9±11 | 100 | +8±3* | +41±19 |
| (10) HbO ₂ артериальной крови, % | 100 | +14±7 | -31±12* | 100 | +1±3 | -37±11* |
| (11) HbO ₂ оттекающей от мозга венозной крови, % | 77±1,9 | -2±1 | -3±3 | 71±2,7 | +1±1,6 | +6±4 |
| (12) Артериовенозная разность по HbO ₂ , % | 49±2,6 | +2±0,5* | -10±3* | 49±3 | -1±1 | -10±7 |
| (13) Артериальное давление, мм рт. ст. | 28±1,9 | -9±5 | +17±9 | 22±2,8 | +4±5 | +57±17* |
| | 109±11 | +3±0,9* | -21±3,6* | 98±9 | -4±3 | -27±6* |

key:

1. Index
2. Intact animals (10 experiments)
3. Initial data
4. Time of injection
5. Min
6. Acute intoxication by chlorophos (nine experiments)
7. Volumetric blood flow rate from confluence of brain venous sinuses, ml/min
8. Brain oxygen absorption, percent
9. Brain oxygen tension, percent
10. HbO₂ of arterial blood, percent
11. HbO₂ of venous blood draining from brain, percent
12. Arterial-venous HbO₂ concentration difference, percent
13. Arterial pressure, mm Hg

Brain oxygen consumption decreases in response to benactyzine in animals intoxicated by chlorophos, and it increases when spasmolytin is injected. In this case following spasmolytin injection, in most experiments brain circulation decreases, while use of benactyzine causes circulation to change biphasally. Perhaps the positive effect of benactyzine seen in the presence of intoxication by organophosphoric compounds (7,12), the rise in the central nervous system's resistance to hypoxia and ischemia (11), and the preventive action of benactyzine on development of experimental brain edema (6,8,9,14) are products of not only blockade of the central cholinergic systems but also a decrease in utilization and consumption of oxygen by the brain. This cannot be said in relation to spasmolytin, since utilization of oxygen by the brain of intact dogs and consumption of oxygen in animals intoxicated by chlorophos increase when spasmolytin is employed.

The increase of volumetric blood flow we revealed in most experiments during the first few minutes following benactyzine injection can be explained by a number of factors. On one hand it might be associated with its spasmolytic action (4,5), while on the other hand it might be associated with change in the gas composition of blood, an increase in the PCO_2 and a decline in the PO_2 . A decline in saturation of arterial blood by oxygen coupled with a simultaneous decrease in the amplitude of the respiratory movements of dogs in response to benactyzine had been observed earlier (1). Perhaps the further decline in brain circulation coupled with concurrent decrease in arterial pressure is the result of disturbed autoregulation. The possibility is not excluded that the decline in circulation is associated with an increase in the tone of the internal carotid arteries resulting from dominance of sympathetic over parasympathetic tone in the presence of a blockade of muscarine-sensitive receptors (13), or that it is the result of an increase in norepinephrine excretion in response to benactyzine (5,10). As far as spasmolytin is concerned, according to (13) compounds that block central nicotine-sensitive cholinergic receptors decrease the resistance of the internal carotid arteries. In the opinion of the authors this is associated with the spasmolytic properties inherent to them. It should have been expected that a decline in tone of major blood vessels would lead to a decrease in brain circulation. However, as follows from our data, in response to spasmolytin the brain blood supply of intact dogs significantly decreases following a short-term increase coupled with a concurrent decline in arterial pressure. Apparently the decline in volumetric blood flow rate is the product of disturbed autoregulation and passive change of circulation in brain vessels due to shifts in blood pressure. This hypothesis is entirely valid, since our experiments were conducted under the conditions of deep barbiturate anesthesia, which could disturb autoregulation (15).

Conclusions

1. When injected intravenously, benactyzine (2 mg/kg) and spasmolytin (1 mg/kg) have a biphasal action on brain circulation of anesthetized dogs in most experiments: Following a short-term increase in circulation, a distinct decrease can be noted.

2. The difference in oxyhemoglobin concentration in arteries and veins decreases in response to benactyzine and grows in response to spasmolytin. Consumption of oxygen from the blood changes irregularly.

3. Absorption of oxygen by the brain of dogs intoxicated by chlorophos decreases in response to benactyzine and increases in response to spasmolytin. In this case brain circulation changes biphasally (as is the case with anesthetized dogs), decreasing in most experiments following injection of spasmolytin.

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PHARMACOLOGY

UDC 615.214.24:547.854.5].015.45:612.398.145.1

STUDY OF THE ACTION OF BARBITURIC ACID DERIVATIVES ON THE PHYSICOCHEMICAL PROPERTIES OF DNA

Moscow FARMAKOLOGIYA I TOKSIKOLOGIYA in Russian No 3, 1978 pp 314-316

[Article by V. S. Kudrin, V. S. Osnyach, and A. I. Matyushin, Department of Molecular Pharmacology and Radiobiology, Biomedical School, Moscow Medical Institute No 2 imeni N. I. Pirogov]

[Text] The action of barbituric acid derivatives--phenobarbital, ethaminal sodium, and amital sodium--on the physicochemical properties of nucleic acids were studied. It is demonstrated that as compared to ethaminal sodium and aminal soldium, phenobarbital has a more pronounced action upon the secondary and tertiary structure of native DNA molecules.

Among compounds producing a dependence, barbituric acid derivatives are of considerable interest. Despite a significant number of works devoted to the mechanism of their action, some stages of this action remain unclear. This pertains first of all to reception of barbiturates and the means of activation of the genome (1). The opinion exists that components of the genome itself and, in particular, nucleic acid molecules may be the barbiturate receptors, interaction with which leads to activation of the genome. Changes in RNA synthesis at the time of barbiturate induction may possibly stem from direct effects of the narcotics on the physicochemical properties of DNA. No data are available in the literature on the action of narcotics in the barbiturate group on the physicochemical properties of DNA. In this connection the objective of our work was to study the action of barbiturate preparations--phenobarbital, ethaminal sodium, and amital sodium--on some DNA characteristics.

Research Methods

DNA preparations isolated from rat liver tissue by Marmur's method (4) were used in the experiments. The concentration of RNA, evaluated according to Schmidt and Tanhauser, and the concentration of protein, determined according to Lowry, did not exceed 1-2 percent in the DNA preparations.

Standard saline solution (0.15 M NaCl + 0.015 M sodium citrate) and weak saline solution (0.015 M NaCl + 0.0015 M sodium citrate) served as the solvent for the analyzed pharmacological compounds and DNA preparations; the solution pH was 7.0.

Ultraviolet absorption spectrums of DNA molecules in the presence of barbiturates were recorded with a Hitachi-323 differential spectrophotometer in the 210-320 nanometer interval.

Thermal denaturation of DNA preparations in the presence of barbiturates was performed in a thermostatic cuvette with an SF-4A spectrophotometer (temperature interval--20-95°C, exposure time at given temperature--5 min). The dependence of optical density on temperature was determined at 260 and 280 nanometers.

Viscosimetric measurements of DNA and barbiturate molecules were made with Ostwald's low-gradient three-ball viscosimeter.

DNA concentration in solution was within 20-50 µg/ml, and the concentrations of phenobarbital, ethaminal sodium, and amital sodium were $5 \cdot 10^{-6}$ - $5 \cdot 10^{-4}$ M. The time of incubation of DNA and barbiturates was 30 minutes.

Results and Discussion

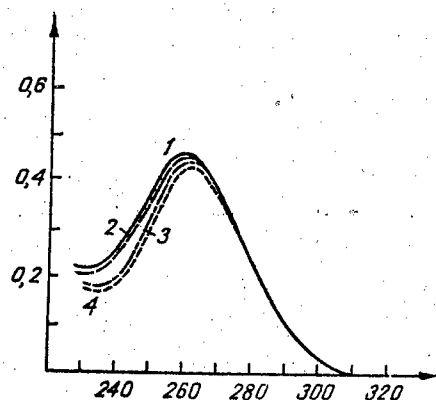
We can see from the table below that ethaminal sodium and amital sodium have practically no effect on the melting point of DNA molecules, while phenobarbital increases it insignificantly. Phenobarbital and ethaminal sodium have about the same effect on characteristic viscosity, increasing it; amital sodium does not produce this effect.

Effect of Barbituric Acid Derivatives on Physicochemical Properties of DNA ($M \pm m$)

| (1) Показатель | Контроль (2) | Фенобарби- тал (3) | Этаминал натрия (4) | Амита-л натрия (5) |
|-----------------------------------|-----------------|--------------------------|---------------------------|--------------------------|
| (6) Температура плавления, град.: | | | | |
| (7) аденин-тимин-пары | 68,7±0,4 | 69,7±0,2 | 68,2±0,4 | 68,3±0,3 |
| (8) гуанин-цитозин-пары | 69,4±0,5 | 71,3±0,3 | 69,4±0,4 | 70,3±0,3 |
| (9) Характеристическая вязкость | 125,8±4,5 | 136,0±1,0 | 138,0±6,0 | 127,7±6,9 |

Key:

- | | |
|---------------------|-----------------------------|
| 1. Index | 6. Melting point, degrees: |
| 2. Control | 7. Adenine-thymine pairs |
| 3. Phenobarbital | 8. Guanine-cytosine pairs |
| 4. Ethaminal sodium | 9. Characteristic viscosity |
| 5. Amital sodium | |



Effect of barbituric acid derivatives on spectral characteristics of DNA: Abscissa--wavelength (nanometers); ordinate--optical density (units); 1--control; 2--ethaminal sodium; 3--amital sodium; 4--phenobarbital.

As we know, the melting point and characteristic viscosity characterize the secondary and tertiary structure of macromolecules respectively. Thus significant characteristic viscosity reflects the conformation of biopolymer macromolecules in solution. The conformation of DNA depends primarily on the extent to which macromolecules are structured, as well as on properties of the solvent. The fact that phenobarbital and ethaminal sodium increase the characteristic viscosity of DNA indicates that the DNA shifts to a more rigidly structured state.

Experiments on the action of barbiturates on DNA using the differential ultraviolet spectrophotometry method confirm this hypothesis. As we can see from the figure, all of the studied narcotics elicit hypochromic and bathochromic shifts in the DNA ultraviolet spectrum, the greatest change in the DNA absorption spectrum occurring under the influence of phenobarbital. At the same time we know that a decrease in absorption may indicate an increase in the degree to which DNA molecules are structured.

It follows from data concerning changes in the melting point of DNA in response to barbiturates, except for phenobarbital, that in contrast to the tertiary structure, the secondary structure of DNA apparently experiences insignificant changes.

A typical property of all barbiturates is presence of a negative charge in their molecule when the solution pH is 7.0. As we know, DNA molecules having acid properties also carry a negative charge. Hence it follows that ionic interaction apparently cannot be responsible for the binding of narcotics and DNA, although their influence on physicochemical properties not stemming from direct contact is not excluded.

As we know, selectivity in interaction with molecules having a certain structure and typical chemical groupings is a specific trait of receptor molecules.

The fact that out of the three studied barbiturates phenobarbital was found to be the most active in relation to both the secondary and tertiary structure of DNA can obviously be explained by its pronounced hydrophobic properties (due to presence of a phenyl radical), which is what determines its possible influence on the hydrophobic areas of DNA molecules.

Our data indicating change in the physicochemical properties of DNA in response to narcotics can be explained by results obtained in (2,3), according to which formation of complexes of barbiturates and adenine nucleotides through hydrogen bonds is possible. Such interaction may also alter the extent to which DNA molecules are structured, which would lead to change in the physicochemical properties of DNA. For the moment it is difficult to say whether or not such interaction, which is seen in experiments with individual nucleotides, occurs in the whole DNA molecule.

Summarizing the above, we can conclude that specificity is absent in the action of ethaminal sodium and amital sodium on the secondary and tertiary structure of DNA molecules. In contrast to these barbiturates, phenobarbital causes change in both the secondary and tertiary structure of the macromolecules. The possibility is not excluded that being the strongest, among all barbiturates, inducer of protein and nucleic acid synthesis, the action of phenobarbital is associated with changes it produces in the physicochemical properties of DNA.

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PHARMACOLOGY

UDC 616-006-02:616.217.34

THE POSSIBILITY OF NEUROPHARMACOLOGICAL REGULATION OF CHEMICAL CARCINOGENESIS INDUCED BY DIETHYLNITROSAMINE

Moscow FARMAKOLOGIYA I TOKSIKOLOGIYA in Russian No 3, 1978 pp 338-341

[Article by V. K. Gurkalo and M. A. Zabezhinskiy, Laboratory of Chemical Carcinogenic Agents, Institute of Oncology imeni N. N. Petrov, USSR Ministry of Public Health]

[Text] Pharmacological, morphological, and biochemical techniques were used to analyze the action of a number of neurotropic agents on chemical carcinogenesis induced by diethylnitrosamine (DENA). Atropine significantly stimulated carcinogenesis in the liver and esophagus of experimental animals, while α -adrenoblocking agent, a pyrrhoxane analog, and especially proserine inhibited these processes. A statistically significant rise in activity of mitochondrial monoaminoxidases in liver cells was noted in all rats receiving DENA. Information presented in this communication, data acquired earlier concerning the stimulatory action of exogenous norepinephrine on carcinogenesis, and published data on the carcinogenic action of neurotropic agents and their carcinogenesis-modifying action permit formation of a conception concerning the triggering role of catecholamines in cell transformation occurring in carcinogenesis induced by DENA.

We know that some neurotropic agents have carcinogenic properties--urethane, reserpine, and others (3,9), that they increase the frequency with which spontaneous tumors are formed--phenobarbital (7,10,12), and that they have a modifying influence on chemical carcinogenesis and growth of grafted tumors--ganglioblocking agents, aminazin, phenobarbital, dibenamine, and others (1,2,11,13). Nevertheless the role of the nervous system and especially of its functional components in blastomogenic transformation has not been studied as yet.

The goal of the present study was to analyze the effect, upon chemical carcinogenesis, of a number of neurotropic preparations acting at adrenergic and cholinergic synapses, and to study the activity of one of the components

in the biogenic amine degradation system--mitochondrial monoaminoxidase (MAO) in liver cells (5).

Research Methods

Diethylnitrosamine (DENA) was selected as a chemical carcinogen causing formation of tumors in the rat liver and esophagus. The experimental rats were subdivided into four groups containing 15 animals each. All animals received DENA with drinking water (100 mg/liter). Rats in group 1 received physiological solution subcutaneously (0.2 ml) three times a week throughout the entire experiment; rats in group 2, 3, and 4 were given atropine (12 mg/kg), proserine (15 µg/kg) and α -adrenoblocking agent--a derivative of 3-phenylpyrrolidone containing a γ -aminoketo group (25 mg/kg) (6) respectively, subcutaneously at the same frequency and with the same volume of physiological solution. Six months after the start of the experiment the animals were killed, and the liver and esophagus were subjected to morphological analysis. MAO activity in recently isolated liver cell mitochondria was determined in intact and experimental rats (8) using serotonin and norepinephrine as the substrates.

Results and Discussion

The results of the experiments on the effect of neurotropic preparations on the frequency and quantity of tumors in the liver and esophagus resulting from DENA injection are shown in Table 1. At the selected dose, in the control group the carcinogen elicited hepatocellular cancer in about 50 percent and esophageal tumors in 20 percent of the animals. Columns 6 and 10 in Table 1 show parameters characterizing the dimensions and quantity of carcinogenic changes in the liver and esophagus of rats in this group. Injection of atropine, which is an antagonist to acetylcholine--the mediator of cholinergic nerve fibers, significantly stimulated the frequency of arisal of tumors both in the liver and esophagus (see Table 1, columns 8, 9, 12, and 13). However, the multicentric nature of carcinogenic changes did not differ from those in the control group. As with pyrrhoxane, which had been studied earlier (4), α -adrenoblocking agent used in the present work had practically no influence on the frequency of arisal of tumors as compared to control, and it significantly decreased the multicentric nature of tumor growth in both the liver and esophagus (see Table 1, columns 6 and 10).

Use of proserine, an inhibitor of acetylcholine degradation, significantly decreased both the frequency and quantity of tumors in the liver and esophagus (see Table 1, columns 4, 5, 6, and 10).

The results of research on the MAO activity of mitochondria in liver cells at the end of the experiment are shown in Table 2. On comparing these data with the control group (intact animals of corresponding age) we noted a statistically significant rise in the enzyme's activity, as determined with two substrates.

Table 1. Effect of Neurotropic Preparations on Frequency and Quantity of Carcinogenic Changes Following Injection of Diethylnitrosamine (DENA) into Rats.

| (1) Условия опыта | (2) Число животных | | (3) Число животных с опухолями | | (4) Выраженность морфологических изменений | | | | | | | | |
|-----------------------------|-----------------------|----|-----------------------------------|---|--|---------------|--|--------------------------------|-----------------|----------------------------|--|----------------------------------|----------------|
| | (9) в начале опыта | | (10) в конце опыта | | (5) в печени | | | | (6) в пищеводе | | | | |
| | | | | | (7) макроскопия | | (8) гистологическое исследование | | (7) макроскопия | | (8) гистологическое исследование | | |
| | | | | | (11) печени | (12) пищевода | (13) число баллов на 1 животное с опухолью ($M \pm m$) | (14) пролиферативные изменения | (15) аденомы | (16) гепатоцеллюлярный рак | (17) число баллов на 1 животное с опухолью ($M \pm m$) | (18) гиперпластические изменения | (19) папилломы |
| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | |
| (20) ДЭНА | 15 | 15 | 7 | 3 | 3,2±0,3 | 10 | 6 | 7 | 2,0±0,41 | 5 | 3 | 2 | |
| (21) ДЭНА и атропин | 15 | 13 | 12 | 7 | 2,7±0,17 | 13 | 12 | 11 | 1,8±0,30 | 9 | 7 | 6 | |
| (22) ДЭНА и прозерин | 15 | 11 | 2 | 1 | 1,5 | 6 | 1 | 2 | 1,0 | 3 | 1 | — | |
| (23) ДЭНА и адрено-блокатор | 15 | 12 | 6 | 2 | 1,7±0,18 | 8 | 1 | 5 | 1,0 | 6 | 2 | 1 | |

Note: Macroscopic assessment of the quantity and size of tumorous nodes is in points: 1 point--singular (up to 5 in each lobe) tumorous nodes (0.1-0.2 gm); 2 points--multiple (more than 5 in each lobe) tumorous nodes (0.3-0.5 cm); 3 points--multiple (0.3-0.5 cm) or singular (0.6-1 cm); 4 points--multiple (0.6-1 cm) or singular (greater than 1 cm); 5 points--multiple (greater than 1 cm).

Key:

- | | |
|--|--|
| 1. Experimental conditions | 13. Number of points per animal with tumor ($M \pm m$) |
| 2. Number of animals | 14. Proliferative changes |
| 3. Number of animals with tumors | 15. Adenomas |
| 4. Expression of morphological changes | 16. Hepatocellular cancer |
| 5. In liver | 17. Hyperplastic changes |
| 6. In esophagus | 18. Papillomas |
| 7. Macroscopic | 19. Cancer |
| 8. Histological analysis | 20. DENA |
| 9. At start of experiment | 21. DENA and atropine |
| 10. At end of experiment | 22. DENA and proserine |
| 11. Liver | 23. DENA and adrenoblocking agent |
| 12. Esophagus | |

Table 2. Monoaminoxidase (MAO) Activity of Mitochondria Recently Isolated From Experimental Rat Liver Cells.

| Условия опыта (1) | Число опы- тов (2) | Активность MAO, мкг NH ₃ на 1 мг митохондриального белка за 1 ч инкубации (3) | |
|---------------------------------|-----------------------|--|----------------------------------|
| | | с норадрена- лином (10 мкМ) (4) | с серотонином (10 мкМ) (5) |
| (6) Возрастная норма | 12 | 2,0±0,36 | 2,7±0,18 |
| (7) ДЭНА | 15 | 3,47±0,23* | 3,85±0,30* |
| (8) ДЭНА и атропин | 13 | 3,2±0,17* | 3,7±0,25* |
| (9) ДЭНА и прозерин | 11 | 3,4±0,29* | 4,07±0,19* |
| (10) ДЭНА и адрено- блокатор | 12 | 2,65±0,18 | 3,6±0,27* |

Note: Asterisks indicate statistically significant differences from normal ($P \leq 0.05$).

Key:

- | | |
|--|-----------------------------------|
| 1. Experimental conditions | 5. With serotonin (10 μ M) |
| 2. Number of experiments | 6. Developmental norm |
| 3. MAO activity, μ g NH ₃ per mg mitochondrial protein per hour of incubation | 7. DENA |
| 4. With norepinephrine (10 μ M) | 8. DENA and atropine |
| | 9. DENA and proserine |
| | 10. DENA and adrenoblocking agent |

Using a similar carcinogenesis model, we had demonstrated earlier that injection of exogenous norepinephrine significantly stimulated formation of liver tumors while injection of the adrenoblocking agent pyrrhoxane inhibited it (4). The inhibitory effect another α -adrenoblocking agent--dibenamine--has on liver carcinogenesis was reported in (13). Results presented in this communication and obtained earlier can be explained on the basis of the same conception by hypothesizing that blastomogenic transformation of hepatocytes in the liver and epithelial cells in the esophagus in response to DENA is under central nervous system control. In this case cholinergic influences inhibit while adrenergic influences stimulate carcinogenesis. In these conditions the action of the cholinolytic atropine cancels the inhibitory effect of the cholinergic component, and the stimulatory action of endogenous norepinephrine manifests itself on the background of sensitization of adrenoreceptors by the carcinogen, which expresses itself as an increase in the frequency of liver and esophageal tumors. Data acquired following injection of exogenous norepinephrine and α -adrenoblocking agents can be explained in the same fashion. In our opinion the limited influence of central α -adrenoblocking agents on the frequency of arisal of tumors can be explained by both their insufficient organotropism and their swift elimination from the body.

Proserine, a cholinesterase inhibitor which intensifies the effect of endogenous acetylcholine, significantly inhibited carcinogenesis, which indicates antagonism between cholinergic regulatory effects and the carcinogenic effect of DENA.

The rise in the deaminating activity of mitochondrial MAO also indicates that catecholamines have an important role in blastomogenic transformation of liver and esophageal cells. An increase in the tone of the cholinergic component in response to administration of both proserine and adrenoblocking agents on the background of a persistently high activity level of intracellular MAO causes development of tolerance of the DENA target cells to the damaging action of catecholamines.

This conception is to be treated as a working scheme. It pertains to a concrete model, and it is based on morphopharmacological analysis of the obtained data. In order to expand and deepen our ideas concerning the role of neurogenic factors in arising of cancer, we must do more research with different neurotropic preparations using different models of carcinogenesis.

Conclusions

1. The modifying action of neurotropic preparations attests to the important role of the nervous system in achieving the blastomogenic effects of diethylnitrosamine (DENA).
2. Intensification of cholinergic influences inhibits carcinogenesis in the liver and esophagus when DENA is administered.
3. Stimulation of carcinogenesis by administration of preparations intensifying the tone of adrenergic nerve fibers and the increase in deaminating activity of mitochondrial monoaminoxidase in liver cells indicate participation of monoaminergic structures in blastomogenic transformation of liver and esophageal cells.

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CSO: 1870

PHARMACOLOGY

UDC 615.917'22.085.241:547.478.6

CYSTEINE ACTIVITY IN ANIMALS INTOXICATED BY DIFFERENT HALOID HYDROCARBONS IN THE ALIPHATIC SERIES

Moscow FARMAKOLOGIYA I TOKSIKOLOGIYA in Russian No 3, 1978 pp 342-344

[Article by G. V. Bakhishev, Laboratory of Experimental Therapy, All-Union Scientific Research Institute of the Hygiene and Toxicology of Pesticides, Polymers, and Plastics]

[Text] It was established through intoxication of rats by different haloid hydrocarbons of the aliphatic series (LK₉₉ and LD₉₉) that the free amino acid cysteine is a group antidote to intoxication of animals by monohaloid hydrocarbons. It is demonstrated that the therapeutic activity of cysteine depends not on the nature of the haloid and the double bonds but rather on the quantity of haloid atoms in the molecule, the length, the ramifications, and the nature of the radical.

It is established that the cysteine salts acetylcysteine and glutathione have sufficient therapeutic activity. When rats are intoxicated by haloid alkyls, dithiol antidotes (mecaptide, BAL) and other tested therapeutic preparations were proven to be ineffective.

Haloid hydrocarbons in the aliphatic series are extensively employed in the national economy and at home. Cases of human intoxication are possible due to their specific physicochemical properties (volatility, reaction capability) and high toxicity. We do not as yet have specific agents with which to treat intoxications by these compounds.

It was established earlier that cysteine has high therapeutic activity against intoxication by methyl bromide, and it was hypothesized that free cysteine and its derivatives may turn out to be effective against animal intoxications by various haloid hydrocarbons in the aliphatic series (G. N. Bakhishev, 1972). The present work is devoted to clarifying this hypothesis.

Research Methods

A process developing in animals (rats) subjected to inhalational intoxication (static poisoning during a 30 minute exposure) served as the model of intoxication. Haloacetic acids and chloroacetic acid ethers were injected intraperitoneally. Therapeutic preparations (free cysteine, acetylcysteine, glutathione, cysteine salts, penicillamine, and others) were injected intragastrically or subcutaneously in the form of 1-5 percent aqueous solutions.

Cysteine and the other preparations were used in accordance with the most optimum scheme (150 mg/kg subcutaneously 30 minutes before and 5 minutes after intoxication)--that is, with a therapeutic-preventive goal--to reveal therapeutic activity. Later we separately studied the protective and therapeutic activity of preparations which had an effect in these conditions. For protective purposes the preparations were injected intragastrically at a dose of 750 mg/kg, and sometimes 500 mg/kg 30 minutes prior to intoxication. Preparations (cysteine, acetylcysteine, glutathione) were injected for therapeutic purposes repeatedly--5 minutes and 1 and 3 hours after intoxication at doses of 300, 200, and 100 mg/kg. Observations were taken for 2-3 weeks. There were from 12 to 48 rats in each group.

The table below shows the chemical formulas and toxicity data for haloid hydrocarbons differing in the nature of the haloid and radical, as well as in the number of haloid atoms per molecule. The therapeutic activity of cysteine and other therapeutic preparations was studied on rats intoxicated by these compounds. The table below presents information only on cysteine activity. The effectiveness of other preparations is described below.

Results

The table shows data on the therapeutic-preventive, protective, and therapeutic activity of cysteine in rats intoxicated by different haloid hydrocarbons in the aliphatic series.

Analysis of the therapeutic-preventive activity of cysteine revealed that free cysteine has pronounced activity when animals are intoxicated by compounds containing one atom of chlorine, bromine, and iodine. In this case cysteine activity decreases somewhat in homologous series containing an atom of bromine and iodine. Introduction of double bonds (allyl bromide) or addition of CO₂ (methyl bromide and methallyl chloride) has almost no effect on the therapeutic-preventive activity of cysteine. Addition of a second haloid atom to the molecule causes a decline (methylene chloride) or complete loss (dibromomethane) of cysteine activity. When rats are intoxicated by compounds containing an epoxy group (epichlorohydrin) or an acid group (haloacids) the activity of cysteine once again decreases somewhat or drops dramatically (monochloroacetic acid). Introduction of three or four chlorine atoms or an ether group as well as isoforms (isopropyl and isobutyl iodide) into the toxic molecules causes complete loss of cysteine activity (see table).

**Therapeutic Activity of Cysteine in Rats Intoxicated
by Different Haloid Hydrocarbons in the Aliphatic Series**

| (1) Соединение | (2) Химическая формула | (3) LK ₅₀ , мг/л | (4) Активность цистеина, % выживаемости животных | | |
|---|---|--------------------------------|---|-----------------|-----------------|
| | | | (5) лечебно-профилактическая | (6) защитная | (7) лечебная |
| (8) Хлористый метил | CH ₃ Cl | 200 | 100,0 | 93,4 | 83,4 |
| (9) Хлористый метилен | CH ₂ Cl ₂ | 124 | 50,0 | | |
| (10) Хлороформ | CHCl ₃ | 142 | 0 | | |
| (11) Четыреххлористый углерод | CCl ₄ | 138,7 | 0 | | |
| (12) Эпихлоргидрин | C ₃ H ₅ OCl | 20,8 | 66,6 | | |
| (13) Металлилхлорид | C ₄ H ₇ Cl | 67,1 | 100,0 | 100,0 | 83,4 |
| (14) Металлилхлорид + CO ₂ | | 53,7 | 83,4 | 100,0 | 75,0 |
| (15) Бромистый метил + CO ₂ | | 9,4 | 89,0 | 83,4 | 83,4 |
| (16) Бромистый метил | CH ₃ Br | 12,5 | 98,0 | 86,8 | 75,0 |
| (17) Бромистый этил | C ₂ H ₅ Br | 370 | 83,4 | 66,6 | 53,4 |
| (18) Бромистый пропи́л | C ₃ H ₇ Br | 369 | 83,4 | 66,6 | 41,5 |
| (19) Бромистый бути́л | C ₄ H ₉ Br | 386 | 75,0 | 50,0 | 33,3 |
| (20) Бромистый алли́л | C ₃ H ₅ Br | 14,8 | 91,7 | 75,0 | 66,6 |
| (21) 1,2-Дибромэтан | C ₂ H ₄ Br ₂ | 22,3 | 0 | | |
| (22) Иодистый метил | CH ₃ I | 12,0 | 100,0 | 75,0 | 83,4 |
| (23) Иодистый эти́л | C ₂ H ₅ I | 91,4 | 91,7 | 66,6 | 91,7 |
| (24) Иодистый пропи́л | C ₃ H ₇ I | 108,6 | 83,4 | 50,0 | |
| (25) Иодистый изопропи́л | | 345 | 0 | | |
| (26) Иодистый бути́л | C ₄ H ₉ I | 527 | 75,0 | 50,0 | |
| (27) Иодистый изобути́л | | 310 | 0 | | |
| (28) Монохлоруксусная кислота | ClCH ₂ COOH | 154 | ЛД ₅₀ (33) мг/кг (34) 16,6 | | |
| (29) Монобромуксусная кислота | BrCH ₂ COOH | 114 | 50,0 | | |
| (30) Моноиодуксусная кислота | ICH ₂ COOH | 94 | 75,0 | | |
| (31) Метилловый эфир хлоруксусной кислоты | ClCH ₂ COCH ₃ | 78,1 | 0 | | |
| (32) Этиловый эфир хлоруксусной кислоты | ClCH ₂ COC ₂ H ₅ | 138,7 | 0 | | |

Key:

- | | |
|--|---------------------------------------|
| 1. Compound | 18. Propyl bromide |
| 2. Chemical formula | 19. Butyl bromide |
| 3. mg/liter | 20. Allyl bromide |
| 4. Cysteine activity, % animal survival | 21. 1,2-dibromomethane |
| 5. Therapeutic-preventive | 22. Methyl iodide |
| 6. Protective | 23. Ethyl iodide |
| 7. Therapeutic | 24. Propyl iodide |
| 8. Methyl chloride | 25. Isopropyl iodide |
| 9. Methylene chloride | 26. Butyl iodide |
| 10. Chloroform | 27. Isobutyl iodide |
| 11. Carbon tetrachloride | 28. Monochloroacetic acid |
| 12. Epichlorohydrin | 29. Monobromoacetic acid |
| 13. Methallyl chloride | 30. Monoiodoacetic acid |
| 14. Methallyl chloride + CO ₂ | 31. Methyl ether of chloroacetic acid |
| 15. Methyl bromide + CO ₂ | 32. Ethyl ether of chloroacetic acid |
| 16. Methyl bromide | 33. LD ₅₀ |
| 17. Ethyl bromide | 34. mg/kg |

Research on the protective and therapeutic activity of cysteine separately established that it is highly effective in animals intoxicated by some monohaloid hydrocarbons in the aliphatic series.

It was also established that under these conditions free cysteine derivatives--acetylcysteine, glutathione, and cysteine salts (sodium, potassium, and calcium)--have sufficient therapeutic activity. Hydrochloric cysteine, D-penicillamine, and cysteine ethers exhibit a certain amount of activity. All other therapeutic preparations, even highly potent dithiol antidotes such as unithiol, mecaptide, and BAL, as well as preparations recently synthesized, did not exhibit therapeutic activity in rats intoxicated by these compounds.

Discussion of Results

The therapeutic activity of cysteine and its derivatives in animals intoxicated by monohaloid alkyls obviously depends on a number of factors. We established that when animals are intoxicated by methyl bromide, methyl iodide, and methallyl chloride the concentration of SH groups in blood and in the liver decreases, while when cysteine is used in the therapy it undergoes normalization. Moreover we know from published information that enzymes in the glutathione-S-alkyltransferase group take an active part in the transfer of alkyl radicals of haloid hydrocarbons in the aliphatic series (1,2). These enzymes transport the alkyl radical to the SH group on glutathione or cysteine. We also know that monohaloid alkyls have a greater reaction capability than do polyhaloid hydrocarbons. We suggest on the basis of the above that the therapeutic activity of cysteine and its derivatives manifests itself in the following: 1) They enter into direct chemical interaction with the toxins; 2) they are alkylated by glutathione-S-alkyltransferase enzymes; 3) they promote synthesis of glutathione when it is blocked by alkylated compounds. We do not exclude participation of all of the variants stated above in detoxification of alkylated compounds in the body. Apparently they all participate, but the principal pathway for detoxification of these toxins is transfer of radicals by enzymes.

The other therapeutic preparations we studied did not exhibit activity, even though they contained highly reactive SH groups, obviously because they are not alkylated by these toxins and are not the substrate for the enzymes.

Conclusions

1. It is established that free cysteine is a group antidote in animals intoxicated by some monohaloid hydrocarbons in the aliphatic series.
2. The therapeutic activity of cysteine does not depend on the nature of the haloid and on double bonds, depending instead on the number of haloid atoms and on the length, ramifications, and nature of the radical.

3. Cysteine derivatives have a certain amount of therapeutic activity.

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CSO: 1870

TOXICOLOGICAL PROPERTIES OF THE DRUG CEPHEDRINE

Moscow FARMAKOLOGIYA I TOKSIKOLOGIYA in Russian No 3, 1978 pp 345-347

[Article by V. G. Pashinskiy, T. M. Vysokovskiy, Zh. N. Khliyenko, A. K. Aref'yeva, L. V. Ponomareva, G. A. Fil'tsanova, T. V. Romanova, V. G. Motov-
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[Text] The drugcephedrine, an antidepressant, has mildly acute and chronic toxicity in experimental conditions; it does not affect the allergic reactions in guinea pigs, it changes the EKG little, and it does not possess teratogenic and embryotoxic properties. In a subtoxic dose it is capable of eliciting dystrophic changes in individual cortical neurons and subcortical formations of the central nervous system, and of delaying embryo growth, especially when administered in the second half of pregnancy.

Cephedrine (1-phenyl-2-[methyl-(β -cyanethyl)-amino]-propanol-1), which was synthesized at the Kazakh SSR Academy of Sciences Institute of Chemical Sciences, has been permitted for use in clinical tests as an antidepressant by the Pharmacological Committee of the USSR Ministry of Public Health. In animal experiments its action is similar to that of imipramine, manifesting antagonism to the central effects of reserpine and potentiating the effect of phenamine (D. V. Sokolov et al., 1975). The objective of this work was to study its toxicity in experiments with one-time and long-term administration.

Research Methods

Acute daily toxicity was determined on mice, rats, and guinea pigs. The LD₅₀ was computed according to Lichfield and Wilcoxon. The toxic action of cephedrine prescribed for a long period of time (2-6 months) was assessed in experiments on dogs, guinea pigs, and rats. The preparation was administered daily in doses of 10-150 mg/kg through a probe into the stomach in the form of a starch suspension (guinea pigs and rats), or it was given with a small quantity of food (dogs). The animals were examined prior to administration

of cephedrine, during it, and at the end of the experiment. Biochemical analyses, study of the composition of peripheral blood, and morphological research were performed according to commonly accepted methods. Thus the bromsulphalein test was performed according to Tugarinova, excretion of urobilin with urine was determined according to Florance, the activity of aspartate- and alanine-aminotransferase in blood was determined according to (Reytman) and (Frankel'), excretion of creatinine with urine was determined according to Folin, protein concentration was determined according to Lowry, residual blood nitrogen was determined according to Rappoport, and blood sugar was determined according to Hagedorn and Jensen. The effect of cephedrine on the intensity of the allergic and inflammatory reactions in guinea pigs elicited by Freund's adjuvant was studied in relation to one-time local administration together with the adjuvant and 2-week administration into the stomach. The effect of the drug on the fetus was studied in experiments on pregnant rats given a 600 mg/kg dose of this drug once between the first and 16th days of pregnancy. Cardiac function was assessed according to EKG data (1), thermoregulation and movement coordination were analyzed, and the effect of the drug on development of a conditioned defensive reflex was determined in the course of prolonged administration of cephedrine.

The numerical research results were treated statistically. During the experiments all animals were on a stable water and food ration.

Results

The LD₅₀ of cephedrine in 14 days of observation following internal administration was 465 (358-605) mg/kg for mice, 940 (790-1,119) mg/kg for rats, and 1,200 (845-1,704) mg/kg for guinea pigs. The cephedrine intoxication pattern exhibited a combination of the times of both arousal and inhibition of the central nervous system. Death of animals from toxic doses of the drug was noted as a rule within the first 2 days after administration. The acute toxicity of cephedrine is lower than that of imipramine.

No deviations were observed in overall condition and behavior of rats given the drug for 4 months (30 and 150 mg/kg) and of guinea pigs given the drug for 2 months (20 and 75 mg/kg). Fur cover and visible mucous membranes remained unchanged. A slight decrease in the weight gain of animals receiving the drug at a large dose was recorded.

When administered over a long period of time, cephedrine did not elicit significant disturbances in the functional state of the liver (the bromsulphalein test and excretion of urobilin with urine for rats, and the activity of aspartate- and alanine-aminotransferase in blood for dogs). Kidney function (level of spontaneous urination and excretion of creatinine and protein with urine for rats, and the concentration of blood residual nitrogen for dogs and rats) did not differ from control either. Administration of a 30 mg/kg dose of cephedrine to rats for 3 months did not have a significant influence on the shape, amplitude, and width of spikes representing atrial and ventricular complexes on the EKG, or on the cardiac contraction rate.

When a dose of 150 mg/kg was administered, some animals revealed a certain decline in cardiac contraction rate and a decrease in P and T spikes; however, the difference was found to be statistically insignificant in comparison of the mean values with control values. The functional state of the body (rectal temperature, capability for maintaining balance on a rotating rod, rate of development of a conditioned defensive reflex) of rats given cephedrine in 30 and 150 mg/kg doses for 3 months did not differ from control.

After prolonged prescription of cephedrine to dogs, rats, and guinea pigs the weight of internal organs (correct per unit body weight) was the same as that of control animals. Rats did not reveal macroscopic and microscopic changes in the spinal cord and brain, lungs, heart, liver, and kidneys. Nor were deviations from normal revealed 2 weeks after administration of the drug was stopped. After 2 months of cephedrine at a dose of 75 mg/kg, three out of eight guinea pigs exhibited moderate hydropic dystrophy of certain neurons in the sixth cortical layer of the temporal and parietal regions, and of some nerve cells in subcortical formations. Other organs and tissues had a normal appearance and structure.

Histomorphological and biochemical analyses (concentration of sugar in blood) did not reveal any sort of significant changes in the function, weight, and structure of endocrine glands (thymus, thyroid, pancreas, kidneys, testes, ovaries). Only some dogs exhibited some stress upon cells in the glomerular zone of the adrenal cortex (light cytoplasm, nuclear hyperchromia).

Cephedrine does not have a local irritating action. Prolonged administration of the drug into the stomach of rats, guinea pigs, and dogs did not produce pathological changes in the mucous membrane of the oral cavity, the pharynx, the esophagus, the stomach, and the small and large intestines. Nor were signs of an irritating action discovered in response to one-time administration of two or three droplets of 10 percent solution into the conjunctival sac of rabbits.

Significant changes were not revealed in the morphological composition of peripheral blood (concentration of erythrocytes, hemoglobin, and leukocytes, ratio of formed elements in white blood, thrombocytes) following 2-6-month administration of cephedrine to dogs, rats, and guinea pigs. The erythrocyte sedimentation rate did not differ from control. The macroscopic and microscopic structure of bone marrow, spleen, lymph nodes, and the thymus remained unchanged. Peripheral blood smears did not reveal pathological forms of leukocytes and erythrocytes.

Cephedrine administered once at a dose of 500 mg/kg into the pad of the paw of guinea pigs and administered for 2 weeks into the stomach at a dose of 20 mg/kg did not intensify the allergic and inflammatory reactions elicited by Freund's adjuvant, even reducing the extent of inflammation somewhat. When cephedrine was administered once to pregnant rats at a dose of 600 mg/kg in the 1st-16th days of pregnancy, developmental disorders were not revealed in fetal organ primordia; cases of embryo death did not increase in frequency.

Only a certain retardation in fetal growth, a decrease in dimensions of a number of hollow bones in particular, was noted. These phenomena were usually observed in the second half of pregnancy.

Conclusions

1. Cephedrine, an antidepressant, is a low-toxicity drug.
2. Arisal of dystrophic changes in the neurons of the cortex and subcortical formations is possible with prolonged administration of cephedrine in sub-toxic doses.
3. Cephedrine does not produce a teratogenic or embryotoxic effect; however, it does somewhat retard fetal growth, predominantly when administered in the second half of pregnancy.

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CSO: 1870

SPECIFIC FEATURES OF THE TOXIC ACTION OF CARBOPHOS ON THE BACKGROUND OF POLYCHLOROPINENE

Moscow FARMAKOLOGIYA I TOKSIKOLOGIYA in Russian No 3, 1978 pp 347-350

[Article by D. I. Sapegin, I. N. Kal'sada, A. G. Kucher, Ye. N. Muntyan, A. A. Rakov, and I. S. Severinov, Department of Hygiene, Crimean Medical Institute]

[Text] The effect of poisoning rabbits *per os* for 21 and 41 days with carbophos (1/25LD₅₀) and its mixture with polychloropinene (cumulative dose 1/25LD₅₀) on the rate of dissociation of oxyhemoglobin and on the concentration of ascorbic acid in blood, liver, kidneys, adrenal glands, and the brain, of thiamine in blood, brain, muscles, and liver, and of copper, manganese, and iron in blood, liver, kidneys, adrenal glands, and brain was studied. Carbophos elicited a significant decline in the oxyhemoglobin dissociation rate and a rise in the concentration of ascorbic acid in brain and blood and of copper in brain, kidneys, and blood. Intoxication by the pesticide mixture was accompanied by a decrease in oxyhemoglobin dissociation rate and an increase in the concentration of vitamin C in blood, of manganese in kidneys, and of iron in striated muscles.

As a rule pesticides are used in various combinations. The clinical pattern of intoxication by poisons with different chemical structure and mechanism of action entering the body simultaneously can differ significantly from the toxic effects of each drug taken separately. In this connection we made it our objective to study the influence of a combination of organophosphoric and organochloride compounds--carbophos and polychloropinene--on the oxyhemoglobin dissociation rate and on the concentration of ascorbic acid in blood, liver, kidneys, adrenal glands, and brain, of thiamine in blood, liver, brain, and striated muscles, and of copper, manganese, and iron in blood, liver, kidneys, muscles, brain, and heart. The results were compared with changes observed upon administration of carbophos alone.

Research Methods

The experiments were conducted with three groups of rabbits. Animals in group 1 (13) received a mixture of carbophos (1/50LD₅₀) and polychlorpinene (1/50LD₅₀) daily, while animals in group 2 (10 rabbits) received carbophos in an amount corresponding to the cumulative dose of the mixture of toxic chemicals (1/25LD₅₀). The pesticides were administered *per os* in the form of a milk emulsion. Animals in the control group (7) received a quantity of pure milk of similar volume. Blood intended for analysis of the oxyhemoglobin dissociation rate and the concentration of vitamins and microelements was taken from the marginal vein of the ear prior to the experiment and 21 and 45 days after the beginning of intoxication. After 45 days of intoxication animals were killed, and tissue concentrations of vitamins and microelements were determined. The oxyhemoglobin dissociation rate was determined by the quick method suggested by Beketov and Sapegin (1), which was significantly improved upon in our previous experiments. Blood ascorbic acid was determined by titration of protein-free plasma with 0.0005 N 2,6-dichlorphenolindophenol (10), and its concentration in organs was determined by the method suggested in (2). Yaksen's method, as modified by Yelisseyeva (3), was used to analyze thiamine in blood and organs. The concentration of copper, manganese, and iron in blood and organs was determined with a quartz spectrograph. Quantitative decoding of the spectrograms was performed with an MF-2 microphotometer. The research results were treated statistically using Student's tables (6).

Results and Discussion

Both carbophos and its mixture with polychlorpinene produced a significant decline in oxyhemoglobin dissociation rate, thus retarding transfer of oxygen from capillary blood to tissues. Different degrees of expression of disturbance in tissue oxygen metabolism are always observed with intoxication by organophosphoric and organochloride compounds. Apparently as a result of hypoxia, the heightened ability of hemoglobin to retain oxygen we revealed has certain significance. The decline in oxyhemoglobin dissociation rate is most highly pronounced with the combined action of carbophos and polychlorpinene. Thus prior to intoxication, the decrease in concentration of oxyhemoglobin in a blood sample placed for 8 minutes in a chamber through which a hypoxic mixture was passed was an average of 7 percent. After 21 days of intoxication by carbophos, statistically significant changes were not observed yet, while when a mixture of carbophos and polychlorpinene was introduced into the body the rate of decline of blood oxygen saturation decreased by 1.65 ± 0.5 percent ($P < 0.01$). After 45 days of intoxication the changes were 2.45 ± 0.7 percent ($P < 0.01$) for carbophos and 4.8 ± 0.8 percent ($P < 0.001$) for the mixture of it and polychlorpinene.

Carbophos intoxication was accompanied by an increase in brain ascorbic acid concentration (21.88 ± 1.41 mg-percent in control, 28.02 ± 0.14 mg-percent in experiments; $P < 0.01$). Its concentration in liver, kidneys, and adrenal

glands did not differ significantly between the experimental group and the control group. Concurrently the concentration of vitamin C in blood increased significantly--by 0.58 ± 0.13 mg-percent ($P < 0.01$) following 21 days of the pesticide's administration, and by 0.21 ± 0.07 mg-percent ($P < 0.02$) following 45 days after administration. Joint administration of carbophos and polychlorpinene elicited a significant rise in ascorbic acid concentration only in blood; this increase was greater than in response to carbophos alone: On the 21st day of intoxication its increase was 0.7 ± 0.1 mg-percent ($P < 0.001$), and on the 45th day it was 0.25 ± 1 mg-percent ($P < 0.05$). Thus polychlorpinene somewhat intensifies the influence of carbophos in this case as well, which was manifested basically 21 days after the beginning of intoxication, when the increase in ascorbic acid concentration was most significant in both groups of animals. Data in (4,5) indicate that vitamin C has a positive effect in the treatment of pesticide intoxications. The authors believe that the increase in blood ascorbic acid concentration is a protective reaction of the body in response to intoxication by poisons, including pesticides. Consequently the more-significant increase in blood vitamin C concentration in response to combined use of carbophos and polychlorpinene attests to higher toxicity of carbophos on the background of polychlorpinene.

Change in blood thiamine concentrations was found to be statistically insignificant in response to administration of both carbophos alone and the pesticide mixture. The concentration of vitamin B₁ in brain, liver, and muscles of animals receiving pure carbophos and carbophos combined with polychlorpinene also did not differ significantly from control.

Study of the effects of the pesticides on blood and tissue microelement concentrations did not reveal significant signs of synergism. Thus statistical treatment of data coupled with application of the methods for determining significant differences in one group of animals failed to confirm significant changes in the concentrations of all three microelements in blood in response to carbophos, as compared to initial levels. When the method for determining significant differences was employed with different groups of animals, a significant difference was revealed in the concentration of copper between experimental and control rabbits after 45 days of intoxication. The copper concentration in control animals was 0.113 ± 0.072 mg-percent at the end of the experiment, while after 45 days of intoxication by carbophos it was 0.641 ± 0.209 mg-percent ($P < 0.05$). In experiments in which animals were intoxicated by the pesticide mixtures, statistical treatment of the data and application of both methods failed to reveal significant changes in the concentration of copper, iron, and manganese in blood.

When carbophos was introduced into the body, there was a significant increase in the concentration of copper in the brain (0.199 ± 0.059 mg-percent in control, 0.673 ± 0.2 mg-percent in experiment; $P < 0.05$) and kidneys (correspondingly 0.61 ± 0.21 and 1.283 ± 0.219 mg-percent; $P < 0.05$). The combination of the analyzed pesticides significantly increased the concentration of manganese in kidneys (correspondingly 0.251 ± 0.077 and 0.588 ± 0.088 mg-percent; $P < 0.01$) and of iron in muscles (0.712 ± 0.315 and 5.131 ± 1.94 mg-percent; $P < 0.05$).

Thus our research showed that polychlorpinene significantly alters the toxic effect of carbophos. According to some indices characterizing the state of oxidative processes in the body (oxyhemoglobin dissociation rate, the concentration of ascorbic acid in blood), these changes manifested themselves in the form of a more-intense response of the body to introduction of the poisons. At the same time a comparison of the effect of carbophos and its mixture with polychlorpinene on blood and tissue microelement concentrations did not reveal signs of synergism. Published data concerning the action of combinations of organophosphoric and organochloride pesticides determined by other tests are contradictory. Thus Stegaylo et al. (7) note that when DDT and chlorophos are introduced into the body simultaneously the former hinders the acetylcholinesterase inactivating action of chlorophos. Such antagonism in action upon cholinesterase between DDT and organophosphoric compounds (chlorophos, thiophos, rogor) was noted by Tostanovskaya et al. (8,9). At the same time, the mixture of DDT and organochloride compounds used in their research elicited significantly more-pronounced microscopic changes in the liver (plethora, vascular thrombosis, protein dystrophy, focal necrosis) than did organophosphoric pesticides alone. Comparing the results of our research with the data of other authors, we can note that the action of a mixture of organophosphoric and organochloride compounds differs significantly from the effect of organophosphoric compounds used alone; however, we cannot confirm presence of synergism or antagonism between them.

Conclusions

1. Intoxication of rabbits by carbophos ($1/25LD_{50}$ *per os* for 45 days) is accompanied by a significant decrease in the oxyhemoglobin dissociation rate and an increase in the concentration of ascorbic acid in blood and brain, and of copper in blood, brain, and kidneys.
2. A mixture of carbophos and polychlorpinene (cumulative dose $1/25LD_{50}$) decreases the oxyhemoglobin dissociation rate and increases the concentration of ascorbic acid in blood, of manganese in kidneys, and of iron in striated muscles.

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CSO: 1870

UDC 615.917'412.232.085.246.9

THERAPEUTIC EFFECTIVENESS OF ACETYLCYSTEINE IN ACUTE DICHLORETHANE INTOXICATION

Moscow FARMAKOLOGIYA I TOKSIKOLOGIYA in Russian No 3, 1978 pp 350-354

[Article by I. G. Mizyukova and M. G. Kokarovtseva, Laboratory of Experimental Therapy, All-Union Scientific Research Institute of the Hygiene and Toxicology of Pesticides, Polymers, and Plastics]

[Text] It is demonstrated that with multiple administration, acetylcysteine has a pronounced therapeutic action against acute intoxication of rats, mice, and rabbits by dichlorethane: Animal survival increases, disturbances in hemopoiesis and in the blood coagulation system are prevented to a significant extent, and toxic lesions of the liver and kidneys are decreased.

Detoxification of some representatives of haloid hydrocarbons in the aliphatic series, including dichlorethane, in the homeothermic body in nature is achieved through formation of mercapturic acids and their precursors. In the case of dichlorethane, the toxin's metabolites rather than the toxin itself enter into enzymatic conjugation with reduced glutathione (7).

It was established earlier in our laboratory that one of the most toxic metabolites of dichlorethane is chlorethanol (ethylenechlorhydrin), which is detected in the blood of rats intoxicated by dichlorethane in as little as 1 hour and in liver in 4 hours after administration of the toxin, and it continues to be detected for the first 2 days of intoxication. It has also been demonstrated (3) that some thiol compounds have a certain therapeutic effect in acute intoxication of rats with chlorethanol.

In comparative analysis of the possible therapeutic effectiveness of thiol compounds (free cysteine, manganese and calcium salts of cysteine, cysteine asparginate, glutathione, acetylcysteine) in the conditions of acute dichlorethane intoxication, special attention should be turned to acetylcysteine in view of its therapeutic activity, low toxicity, stability, the possibility for intravenous injection, and so on.

Acetylcysteine was synthesized at the Latvian SSR Institute of Organic Synthesis, and it has been used to date as a mucolytic agent. Subsequent research on this drug was directed at studying its therapeutic effectiveness against acute dichlorethane intoxication. Specific resources for treating intoxications by this poison are absent.

Research Methods

The research was conducted with 224 animals--114 rats, 60 mice, and 50 rabbits. The pathological process developing in experimental animals given a single LD₉₉ dose of dichlorethane in the stomach served as the basic experimental model: Rats and mice were given this dose as 20 and 5 percent sunflower oil solutions respectively, while rabbits were given the drug in pure form. Acetylcysteine was administered repeatedly to detoxify chlorethanol formed through dichlorethane metabolism: Intramuscularly and intraperitoneally (10 percent) for rats and mice, and intravenously (5 percent) and intramuscularly (10 percent) for rabbits.

Treatment began 5-10 minutes and 1, 2, and 3-4 hours after administration of the toxin. The following choice of doses and the treatment schemes was found to be the most effective. When the toxin was injected intramuscularly and intraperitoneally, on the first day it was administered five times with 3-hour intervals, and on the second day it was administered twice with a 6-8-hour interval. The first two doses administered were 500 mg/kg, and subsequent doses were 300 mg/kg. In intravenous administration (rabbits), the one-time dose was decreased to 200 mg/kg, and the number of injections was up to four. The morphological composition of peripheral blood and the blood coagulation system were studied by standardized methods commonly accepted in the country, using the Tselleskop-101 automatic electronic counter to count erythrocytes and leukocytes; blood fibrinolytic activity was determined according to A. T. Koval'skiy's method (1). The activity of sorbitol dehydrogenase in blood serum was studied by the method of Sevela and Tovarek (6), and it was expressed in micrograms of fructose per milliliter per minute. We also determined urine clearance (4).

Results and Discussion

The research showed that with multiple administration, acetylcysteine is an effective therapeutic agent against acute intoxication of animals by dichlorethane at the LD₉₉ dose (Table 1). Thus animal survival was 97 percent for rats and 92.2 percent for mice when the drug was injected intraperitoneally, and the figures were 83.3 and 77.8 percent with intramuscular injection. Rabbits exhibited 100 percent survival with both intramuscular and intravenous use. The index of therapeutic effectiveness (intraperitoneal injection) was 1.75 for rats (the LD₅₀ was 760.0±18.87 mg/kg for control animals and 1,330.0±37.7 mg/kg for treated animals). What was important was that acetylcysteine had a pronounced therapeutic effect even in cases where treatment did not begin until 1-2 hours after intoxication (Table 2).

Table 1. Therapeutic Effectiveness of Acetylcysteine (Administration Starting 10 Minutes After Intoxication) Against Acute Intoxication of Rats, Mice, and Rabbits by Dichlorethane.

| (1) Вид животных | (2) Доза яда, мг/кг | (3) Контроль | (4) Введение ацетилцистеина | | |
|---------------------|------------------------|-----------------|--------------------------------|----------------------------------|--------------------------|
| | | | (5) внутри- мышечное | (6) внутри- брюшин- ное | (7) внутри- венное |
| (8) Крысы | 850 | 3/18 | — | 12/12 | — |
| (9) Мыши | 950 | 0/18 | 10/12 | 29/30 | — |
| (10) Кролики | 800 | 1/18 | 10/12 | 29/30 | — |
| | 1375 | 0/5 | 10/10 | — | 10/10 |

Note: Here and in Table 2, the number of surviving animals is in the numerator and the total number of animals is in the denominator.

Key:

- | | |
|-----------------------------|----------------------|
| 1. Animal | 6. Intraperitoneally |
| 2. Toxin dose, mg/kg | 7. Intravenously |
| 3. Control | 8. Rats |
| 4. Acetylcysteine injection | 9. Mice |
| 5. Intramuscularly | 10. Rabbits |

Table 2. Therapeutic Effectiveness of Acetylcysteine Against Acute Intoxication of Rats and Rabbits by Dichlorethane (LD₅₀) When the Therapeutic Agent is Administered Late.

| (1) Вид животных | (2) Доза яда, мг/кг | (3) Контроль | (4) Способ введения ацетилцистеина | (5) Время введения ацетилцистеина после интоксикации | |
|---------------------|------------------------|-----------------|---------------------------------------|---|-------|
| | | | | (6) 1 ч | 2 ч |
| (7) Крысы | 950 | 0/18 | Внутрибрюшинное (9) | 12/12 | 10/12 |
| (8) Кролики | 1375 | 0/5 | Внутримышечное (10) | 5/5 | 4/5 |
| | | | Внутривенное (11) | 5/5 | 5/5 |

Key:

- | | |
|---|----------------------|
| 1. Animal | 6. Hours |
| 2. Toxin dose, mg/kg | 7. Rats |
| 3. Control | 8. Rabbits |
| 4. Means of acetylcysteine administration | 9. Intraperitoneally |
| 5. Time of acetylcysteine administration following intoxication | 10. Intramuscularly |
| | 11. Intravenously |

When acetylcysteine was administered at later times, it did have therapeutic effectiveness, but it was lower (rat survival was 56 percent when acetylcysteine was administered after 3 hours, and 25 percent when it was administered after 4 hours).

When rats were intoxicated with the LD₉₉ dose of dichlorethane (control), following a short time of arousal the animals quickly became sluggish, lay down on their sides, and refused to eat. Clonic convulsions were observed among some rats. Death basically occurred within the first 2 days. The intoxication pattern of treated animals differed dramatically from that of control animals. During the first day the treated animals exhibited the same intoxication symptoms as did control animals, but they were less pronounced; on the second day the rats recovered their mobility and ate readily, and on the third day they differed little from intact animals. Later, throughout the entire time of observation (30 days), their behavior did not differ from that of intact animals.

The effectiveness of using acetylcysteine to treat animals intoxicated by dichlorethane was also confirmed by a study of some hemopoietic indices, the blood coagulation system, toxic lesions of the liver and kidneys, and pathomorphological analysis of these organs in treated and control animals. It was demonstrated (2) that acute intoxication of rats by dichlorethane (LD₅₀) is accompanied by early (in the first and second days) development of anemia coupled with a hemolytic component and disturbances in the blood coagulation system in the direction of development of pronounced hypocoagulation. Acetylcysteine therapy significantly inhibits development of anemia, which is revealed in treated animals only on the 3d-7th days and is weakly pronounced. Frequently pronounced phenomena of hypocoagulation are also exhibited on the 3d day, disappearing completely by the 7th day.

Toxic lesion of the liver resulting from acute dichlorethane intoxication (LD₅₀) was evaluated from the activity of sorbitol dehydrogenase. While it was very low for intact animals (0.46 ± 0.039 μg fructose per ml per min), the activity of the enzyme increased dramatically with acute intoxication by dichlorethane, especially on the 3d day of intoxication (29.6 ± 2.98 $\mu\text{g}/\text{ml}/\text{min}$). Acetylcysteine therapy reduced toxic lesion of the liver significantly. The activity of the enzyme in the serum of treated animals was much lower, being 15.36 ± 2.21 μg fructose per milliliter of serum per minute ($P=0.3$ percent) at the time indicated above.

Acute intoxication of rats by dichlorethane was also accompanied by a decline in the depuration function of the kidneys, manifested as a dramatic increase in the quantity of urine in the blood and a decrease in urine clearance, especially on the 3d day of intoxication. While urine clearance of intact animals was 3.96 ± 0.6 ml/min, it was 0.47 ± 0.26 ml/min ($P<0.61$ percent) on the 3d day of intoxication for animals intoxicated by dichlorethane and 1.26 ± 0.19 ml/min ($P=4$ percent) on the same day for treated animals. In addition anuria developed among intoxicated rats by this time, not being observed in a single case among treated animals.

Pathomorphological analysis (conducted together with Candidate of Medical Sciences O. G. Petrovskaya) of the liver and kidneys of rats intoxicated by dichlorethane and treated with acetylcysteine also indicated significant reduction of the expressiveness of pathological changes observed in these organs following acute dichlorethane intoxication. The decrease in damage to kidney tissue structure was especially pronounced; this has important significance, since the outcome of acute dichlorethane intoxication depends to a significant degree on the functional capability of the kidneys.

Consequently administration of acetylcysteine to animals intoxicated by dichlorethane goes a long way to prevent development of disturbances in hemopoiesis and in the blood coagulation system; it reduces toxic lesion of the liver and kidneys.

In all probability dichlorethane is basically detoxified through acetylcysteine therapy by interaction of the drug with dichlorethane or with its other metabolites formed in the body of homeothermic animals, since acetylcysteine has a pronounced therapeutic effect against intoxication by not only dichlorethane but also chlorethanol; in addition the concentration of chlorethanol in the blood of rats intoxicated by dichlorethane and treated with acetylcysteine decreases dramatically (Table 3).

Table 3. Dynamics of Chlorethanol Concentration in the Blood of Rats Intoxicated by Dichlorethane (LD_{50}) and Treated With Acetylcysteine ($n=6$).

| Срок после введения яда, ч (1) | Количество хлорэтанола в крови, мкг/мл (2) | |
|--------------------------------------|---|--------------------------------|
| | контроль (3) | лечение ацетилцистеином (4) |
| 1 | 5,6 | 9,2 |
| 4 | 67,8 | 7,2 |
| 12 | 37,6 | 12,4 |
| 24 | 14,0 | 6,2 |
| 48 | 8,2 | 0,0 |

Key:

1. Time after administration of the toxin, hours
2. Quantity of chlorethanol in blood, $\mu\text{g/ml}$
3. Control
4. Treated with acetylcysteine

Both acetylcysteine itself and cysteine formed in the body of homeothermic animals through deacetylation of acetylcysteine can apparently interact with chlorethanol (5).

Thus acetylcysteine can be viewed as an effective therapeutic agent having specific action in dichlorethane intoxication.

Conclusions

1. Acetylcysteine is an active therapeutic agent in acute intoxication of animals (rats, mice, rabbits) by dichlorethane, with the intravenous method being the most effective.
2. The therapeutic activity of acetylcysteine against acute intoxication by dichlorethane manifests itself as an increase in animal survival, significant prevention of disturbances in hemopoiesis and in the blood coagulation system, and reduction of toxic lesion of liver and kidneys.
3. The high therapeutic effectiveness of acetylcysteine, its low toxicity, and the good tolerance of animals to the drug permit recommendation of this drug for clinical study of acute dichlorethane intoxication.

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PUBLIC HEALTH

AGROINDUSTRIAL COMPLEXES AND INTERFARM ASSOCIATIONS

Moscow NAUKA I ZHIZN' in Russian No 1, 1978 pp 78-83

[Article by R. Kaganova, Special correspondent of NAUKA I ZHIZN': The Firm 'Omskiy Bekon'--A New Type Of Enterprise]

[Text] Specialization and concentration, the creation of interfarm associations and agro-industrial complexes--one of the directions of modern agricultural production. On the basis of interfarm cooperation in the country large agricultural enterprises are being set up which are extensively introducing new organization of labor and progressive technology.

One such enterprise is the firm "Omskiy bekon" headed by Hero of Socialist Labor, Deputy of the USSR Sumpreme Soviet Artur Petrovich Mayorov. Speaking at the special seventh session of the USSR Supreme Soviet he stated: "Life itself and practice have convincingly indicated the high effectiveness of associations... This with all objectivity is confirmed by the experience accumulated by our special-purpose association 'Omskiy bekon'."

On a hot summer evening the car stopped at the rural square next to the wide light steps smoothly rising to the wide open doors. On the gray, elegant building with wall-type mosaic and foundation of dark stone I read the inscription: "Administration of the Order of Lenin of the Sovkhoz 'Luzinskiy.' Firm 'Omskiy bekon'..."

New polished tables, still smelling of fresh lacquer, and thick bundles of transactions are carried by. In this confusion only the correspondent with the suitcase does not fit. With embarrassment I set it with my eyes down behind the ornamented lattice of the hall. A middle-aged, lean, bespectacled man noticed me. He approached and introduced himself: the general director of the firm Artur Petrovich Mayorov. He opened the door of the nearest room slightly and asked someone:

"Isn't there even one chair here?"

He smiles making a helpless gesture:

"Do not judge us too severely, costs of a new home. We are moving to a new building."

17 April 1973 8 sovkhoses of the Omskaya oblast entered into new inter-relationships and united into a firm in order by common forces to produce more meat, milk and feed. Specialization, concentration and the advances of modern science and technology--this is that foundation on which the new association was built. The sovkhoses that entered it, from the very beginning were strictly divided according to their purpose, and now of the eight farms three--"Luzinskiy," "Achairskiy," and "Pobeditel'" are fattening pigs on an industrial basis. The task of "Novoazovskiy"--to increase the breeding quality of livestock. An in four others--"Poltavskiy," "Krasnogorskiy," "Ukrainskiy," and "Yuzhniy"--grain and milk are produced.

The territory of the firm spreads over 235,000 ha, of them almost 170,000 of plowed fields. The association's pig herd exceeds 180,000 head, almost 9,000 in it are the main sows. Cattle number 36,000 head. In the 4 years of operation as the new "Omskiy bekon" data has been accumulated which indicates the deep vital force and the economic profit of the association of farms on the basis of specialization, concentration, and inter-farm cooperation.

Here are some figures. The "wave" of cattle-breeding production increased from 1973 through 1976 from 25.3 to 47 million R--1.9-fold. The sale of meat to the state in 1976 was 23,347 T, whereby the portion of pork--20,350 T. The sovkhos that has specialized in fattening is responsible for seven times more pigs and 9.3 times more production than any other farm of the Omskaya oblast. The net cost of a centner gain in weight of pork at "Omskiy bekon" is almost three times lower than in other farms, and the mean outlays for the same unit--7.7 man-hours, and of feed--5.6 centners of fodder units, while in the nonspecialized farms of the oblast--21.2 man-hours and 8.4 centners of fodder units. At the best automated enterprise of the firm--the kombinat whose facilities are designed for an annual production of 13,000 T of pork, the outlays of labor and feed per centner gain in weight during fattening of animals are still lower--2.2 man-hours and 4.2 centners of fodder units. One operator serves 3000 fattened animals here.

The creation of the firm has also brought graphic social changes. The Siberian village Luzino is second to none in public welfare. The architecture of the homes in the settlement--of course, with gas, bathroom, central heating, and hot water--is pretty and diverse: you will not enter your neighbor's by mistake, and you will not confuse another's with yours. Recently a department store was built, a bookstore, and a House of Life. But the urban conveniences are combined with the advantages of the country: right beyond the village outskirts--a collective orchard, gardens...

In the administration "Luzinskiy" I was supplied with a report from which it followed that during the last 4 years the workers and specialists of the sovkhos bought 55 motor vehicles, 140 motorcycles and motor scooters. From

this same report it was evident that the people here are well-read and curious: for each family there is an average of five subscription publications. And then I learned that the workers of the sovkhos love the theater, and often go to the oblast center for performances--the sovkhos provides buses for this purpose. Many are themselves able to sing and dance: the sovkhos chorus and dancing group have taken first place many times at the regional reviews. The artists appearing in Omsk do not detour the Luzinskiy Palace of Culture, and find an overcrowded hall of grateful spectators.

It is characteristic that at the kombinat--this leading institution in the firm for fattening pigs--excellent and prestigious conditions have been created for the modern young people: the average earnings of the best operators here--180-200 R, a single-shift working day lasts 8 hours, and people enjoy two free days per week. Here there is no problem of personnel. Twenty-seven employees of the kombinat have higher education, 140--middle, and 40 are studying by correspondence.

Thus, in a short time enormous changes have taken place in all spheres of production and daily life. How was all this accomplished? First of all by the fact that in "Omskiy bekon" the advantages of socialist agriculture are skillfully and energetically employed. By the fact that based on science each working day is filled with inquisitive searching. A lot is prompted by the general director of the firm, Mayorov, who is by essence (he is a candidate of veterinary science) and by his nature--a scientist and researcher. Take only his interest in ethology, a science more and more popular in our time. (Who does not know of the experiments of Konrad Lorenz--one of the founders of this scientific direction?) Mayorov turned its conclusions to the benefit of production: based on the knowledge of animal behavior he created a basically new technology of a powerful enterprise in fattening pigs. Here is one of the examples.

The traditional technology of maintaining pigs--frequent, beginning with a young age, movements from group to group, reformations whose goal is to select young stock equal in physical data--as if especially designed to disrupt from time to time the accustomed way of life of the animals. On the days of reformation the production cycle as though slips--the gains in weight are maintained at zero and the farms lose hundreds of centners of meat.

But are all these movements required? In fact pigs can be kept from birth and until sending to the meat packing plant in their nest. And then, probably one can avoid stress situations? Mayorov asked himself this question many times, digging into the literature on ethology and studying the world experience of the branch. He was faced with starting a new kombinat designed to fatten 120,000 pigs a year--he had to search for something and experiment!

Skilfull experimentation is generally in the tradition of "Luzinskiy." More than 10 years ago the country's first complex for fattening 11,000 pigs was built which was enormous according to the scales of that time. The construction of the complex became a serious practical school for Vasiliiy Stepanovich Barbash who was at that time still a student of the Omsk

Agricultural Institute (now he is the head of the design bureau of the firm). Among the enthusiasts who took up the organization of the first complex were the honored livestock expert of the RSFSR, one of the senior specialists of the sovkhos Petr Kuz'mich Kulemin, honored veterinarian of the RSFSR Fedor Pavlovich Ovcharenko, chief engineer of the sovkhos Vladimir Mikhaylovich Afonin. Grigoriy Yakovlevich Kuz'menko also participated in the first developments, and as a consequence he was named head of the complex, and today heads the kombinat.

Artur Petrovich relied on these and many other specialists when he started the experimental verification of the idea he had on the outlook for nest-type maintenance of pigs to be fattened under industrial conditions of large-scale production.

A test group of young pigs was formed with nest-type maintenance, and it was compared with the standard control where the young pigs as they grew as usual were moved from pen to pen. The increases in weight of the animals under 4 months of age indicated that the game was worth playing. In the group which was maintained traditionally the young pigs did not weigh more than 40-42 kilograms, while those in the test group--48-52. At the next stages of fattening the noted tendency was preserved: the young pigs raised by the traditional method did not add more than 0.5 kilograms of weight per day, while the "nest-type"--600 and more grams. It was decided to switch completely to the new principle of maintaining animals for fattening. In this case the sow having had a litter in the pen within a month leaves it, while the babies remain to grow in their nest in the same place. Only the operators change near them: after a definite time the young pigs become a group for raising, and until age 7 months--a group for fattening.

The breaking with tradition forced a re-examination of the organization of labor, design of the pens, and mechanisms and equipment. Mayorov and the specialists spent day and night with the Omsk designers until they had developed together a new project.

The new technology produced results immediately: the daily average increases in weight of the pigs reached 630 grams, losses in weight were eliminated which were inevitable in the transferring of the animals from group to group, and the waste of livestock was reduced to a minimum.

To those that have visited the large animal husbandry complexes there is nothing unusual about the enormous dimensions of the buildings that are not inferior to plant shops. The kombinat in Luzin is no exception. In each shop designed for 24,000 animals there are 8 isolated sections with pens in six rows. If necessary they can be transformed. A movable dividing enclosure isolates the new young pigs from the sows. The young are heated by rays of an infrared lamp. The floor of the pen is brick and near the rear wall it is pig iron and grilled. The manure that falls through the grill of the pens falls into transverse, and then longitudinal channels, and further into collectors from where it is pumped into the organic fertilizer shops.

In the feed box built into the front wall of the pen there are nine cells--one for each piglet. The food is supplied here by an automatic distributor. It has three bins, two filled with dry combined feed for the mother and piglets, and the third--water that moistens the food when it is brought "to the table." Filled with the mixture the distributor goes around the pens on a rail.

The system of ventilation is original. Air is collected by a so-called intake system, and is removed by a concentrated stream, called jet discharge. The system is very effective, there is practically no odor in the pig sty.

The scales of the firm, and the innovations used here have attracted the attention of scientists, and now "Omskiy bekon" is actively cooperating in the farming contract beginnings with several scientific research institutes.

For the time being it is such. The kolkhoz or sovkhov will conclude an agreement on cooperation with the scientific institution, duly transfer money to it, but expect from it not problem elaborations, but as if corrections of their neglected affairs. What kind of scientific collective will be involved in such work? The firm views its cooperation with the institutes in a completely different way. Here science is faced with the problems on which depend tomorrow's production successes, and which the researchers are already interested in. In addition, the firm is ready not only to materially advance the studies it needs, but also to transfer to the institutes a portion of those profits which the production will obtain from the introduction of the scientists' recommendations.

The firm has precisely such relationships with the Siberian Scientific Research Veterinary Institute. The problems raised by the pig breeding of the firm are so many that half of the institute's laboratories that are conducting a comprehensive search are involved in their solution. One of these problems which has disturbed the world's livestock experts since ancient times is the reproduction of the herd. Another--unstudied diseases of the young. At the firm's assignment the scientists are attentively studying at the kombinat increased waves of morbidity of the young pigs, are comparing different months of the year and groups of different operators, are studying the microflora of the animals, and are tracing the relationship between the condition of the animals and the quality of feed.

The scientists are making virological investigations of the sick animals, isolating the pathogens, preparing a vaccine, and treating the herd with it. The researchers are also interested in how the microclimate of the facility affects the reproductive capabilities of the animals. They plan to investigate the system "kombinat-animals-manure-feed," in order to prevent helminthiasis of the pigs. New treatment and prevention preparations are being sought. From the position of protecting the environment the scientists are studying the microbe composition of the air in the zone of the kombinat.

The direct relationship to environmental protection is also found for such a problem--recovery of the kombinat's effluence. It is accumulated daily no more no less in a quantity of a thousand cubic meters from each of the four shops. How not to permit pollution of the environment? How can the farm utilize this effluence with effect year round? The Siberians know that questions which are difficult for all zones of the country become the most difficult in their severe climate. The All-Union Institute for the Agricultural Use of Waste Water is attempting to find a solution to this problem.

Recently the firm created its own scientific production laboratory that operates as a branch of the All-Russian Scientific Research and Technological Institute of Animal Husbandry. An interesting detail: at the invitation of the firm the laboratory is headed by a scientist who had worked before this in one of the leading institutes of the zone. The Luzinskiy scales and scope entice people!

The subject matter of the laboratory has an applied nature. The scientific employees are faced with defining the best norms and approaches to maintaining the young pigs, sows and boars precisely under the conditions of large industrial production, and making their proposals for the perfection of the pen equipment and mechanization as a whole. The combined feed is intensively studied, its quality is controlled, as well as the composition of microelements and amino acids, fatty acids, and other components.

Working on the problems facing "Omskiy bekon" the laboratory will make recommendations standard for all West Siberia.

Having become acquainted with the organization of affairs at the firm "Omskiy bekon" I was no longer surprised when I learned that in Luzin, this Siberian village, there is an office of scientific and technical information that maintains correspondence with the academic institutes thus joining together the interests of production and science. Nevertheless such a figure is impressive: in the sovkhos office of scientific and technical information there are more than 6,000 books, which are actively read with benefit for production.

In the office of scientific and technical information there are about a hundred readers, and each has his own theme about which he wants to know everything. However if the requested publications are not in the office's own stacks (here over 200 journals and information publications are subscribed to), then the reader is still sure that he will receive the necessary book: through the interlibrary loan system it is requested from wherever you want, from any city in the Union.

"Our specialists have already become accustomed," relates the adviser of the office Gertruda Tikhonovna Borodinovskaya, "to the fact that each morning on their desks there is new literature on the problems they are concerned with."

The firm does not spare money for the development of its information center, it is repaid with interest: for on the basis of progressive ideas and new knowledge that intellectual potential is created without which the modern agricultural enterprise is unthinkable.

They speak a lot about the aesthetics in production. And in the "Luzinskiy" and other sovkhoses of the association they know how the surrounding situation affects the worker, and they know and strive to surround man every day with comfort and suitable beauty.

When in the mornings the buses one after another come to the kombinat with the workers they are met with cheerful music. Melodies sound also during the lunch break, but already now quieter in nature and uniform. At the end of the working day when again scurrying like a shuttle a bus with people that have finished their shift leaves every 15 minutes music starts again--soft, and each one who leaves the passageway is accompanied by the warm words of the slogan: "Thank you for good work!"

At the kombinat irreproachable cleanliness reigns, a business-like style, and economical, but focused on man to the last detail. Such, for example, is one detail. The work outfit which each employee changes into before work and after a mandatory shower is comfortable and attractive, but you will not see here the rubber boots which are included in the regular set at many of the major agricultural enterprises. The people work in shoes and overshoes. This is healthier and more hygienic for the workers.

The cafeteria is tasty and inexpensive. Here the interior is also designed with the desire to provide pleasure to the people. Nearby young birch have been planted entwined with living verdure. Their delicate trunks lighten the smart dining hall.

The control room of the kombinat is the center of the automatic control of the production process with electronics and automation, and tracking isotope devices. The panels are conveniently placed whose multicolored lights give information on the course of work at the kombinat. There is attractive furniture, flowers, and birds in cages whose twittering eases the work tension.

There are flowers not only in the control room, but also wherever according to all old concepts they should not be--in the shop for recovery of manure, and at the treatment facilities. Only men work there. And they are met by a parade of flowering pots, big and bright, hung in one green line. The flowers breathe the same clean air that the people working in the shops do.

And now when the reader has formed if but the most general idea of the firm I would like to relate a little about its general director, Artur Petrovich Mayorov, Hero of Socialist Labor, and deputy of the USSR Supreme Soviet. And not only because he is the head of everything here, but also because this man surprises everyone who gets to know him with his persistent and selfless enthusiasm and enormous efficiency.

Mayorov does not belong to the directors who, by trying to be everywhere and universally give out personal instructions "collect information by their feet." He is basically against such a style of management. Moreover this is impossible given the enormous dimensions of the firm, and it is not necessary

given the modern means of communication. Another matter is the personal impressions and meetings with people at their work sites. They are necessary to the director so that then, in private, having collected his thoughts, he can think about production, and can think responsibly and seriously. To this he devotes his morning time before work by analyzing the current and future matters, by comparing the indices of the farms included in the firm, and by zealously following the reports for other large complexes in the country.

On Mondays Mayorov has a reception day. From the morning those come who have personal business with him. On one of these reception days I was surprised at the age composition of those wishing to be received: almost without exception girls and boys, some with their parents.

"We encourage entrance into the technical schools, schools, and institutes," the secretary explained to me. "The firm has 34 scholarship students in the VUZes alone."

There were also people here a little older, often in families. They were interested in something else: did the firm need workers, what are the conditions, do they have apartments?

The visit was not rapid: the director was interested in the motives for people's actions, and in details.

The production affairs are solved in his office with the same thoroughness. Mayorov does not like to impose his opinion on his subordinates and use power. He quietly and patiently hears out each one and tries to convince you so that his, the director's, idea becomes yours. Mayorov's composure is enviable. He never raises his voice. This is from solicitude for people, and a striving to guard them from nervous strains and negative emotions that lead away from true and consistent solutions.

It is astonishing that with all of his business this man has a fine appreciation and love for nature, notices the finest nuances in animal behavior. But apparently the combination of all of these properties also makes the man a rich and integral character.

We talked about which rules he follows in sitting in the director's place. At the end of the conversation he extended a sheet to me on which was typed: "Code of Business Behavior of Director." I will cite if but the partial contents of this curious document which was developed here at the firm on the basis of a study of the science of management, and which has been printed in 200 copies:

"Do not shout. Few hear a shouting person. Do not interfere in the affairs of the subordinates unless necessary. Be able to give up your incorrect decision. This is more important than false prestige.

Persuade, without using power until all other means have been exhausted. Never get irritated. Have infinite patience. The man who is nervous about a lot of things is a poor director.

Do not be ashamed of elegance.

Do not be afraid of talented subordinates. Give the employees the maximum freedom to achieve the goals of the system. It is harmful and dangerous to pretend to know everything. In a business conversation listen carefully to your interlocutor without interrupting him.

Nothing demoralizes work like attributing the merits of the collective to yourself alone. Be just to the service characteristics of a person even if your attitudes leave much to be desired. Be able to combine humaneness with exactingness. This is the prerequisite for a healthy moral climate in the collective.

Give orders firmly but politely. Politeness, tact, and friendliness--an inherent trait of a good style of management."

The firm--now already a scientific production association that includes, besides production, a scientific research laboratory and a selection-genetic center--is operating at the assigned capacities. It is operating with honor--with the Sign of the CPSU Central Committee and the USSR Council of Ministers, and with the impressive demonstration at the VDNKh [Exhibition of Achievements of the National Economy of the USSR]. But even the overfulfilled tasks no longer satisfy it, and the leaders of the firm persistently seek: what else can we do for the development of production, and how can science help?

PHOTO CAPTIONS

- p 79. This is how one of the sections of the kombinat shop looks. The feed distributor travels along the rails along the pens.
- p 80. The young pigs under infrared lamp. The sow is located beside beyond the enclosure. The young pigs stay in the same pen for fattening, while the sow is moved to another place in the shop for new reproduction.
- p 81. The control room automatically controls the entire kombinat. The control panel is shown in the photograph.
- p 82. General director of the firm "Omskiy bekon" Artur Petrovich Mayorov.

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USE OF ELECTRONIC COMPUTER TECHNOLOGY TO AUTOMATE INFORMATION PROCESSES

Frunze ZDRAVOOKHRANENIYE KIRGIZII in Russian No 2, 1978 pp 59-61

[Article by S.F. Semchenkova, Republic Department of Scientific Medical Information of the Kirgiz SSR Ministry of Public Health]

[Text] The role and the importance of the scientific technical and many other types of information in the working out of practical problems and tasks are defined by the deep sense of the slogan that was originated by our time: "Information--the most important national resource." The separation of information activity into an independent branch was elicited by objective reasons the most important of which are the rapid growth of the volume and number of publications, and the physical impossibility for specialists to become familiar with all the scientific reports they are interested in.

The main sources of information on advances in science in the first place are the periodicals and monographs published in many countries of the world. In the last decades the number of monographs and journals has risen, and continues to grow at rapid rates. Researchers in the field of scientific information believe that the flow of information doubles every 10-12 years. At present in the world 19,000 biomedical journals are published. It should also be noted that the medical researcher is not limited today to the limits of medical journals since problems that are very important for medicine and public health are reflected in the journals on biology, physics, chemistry, and others.

The processing of the avalanche-like growing flows of scientific and technical information long ago became impossible without the use of computer technology. The electronic computer is a universal means of processing information. As its fast operation improved and the volume of information to be processed grew the effectiveness of using the computer to create information retrieval systems (IRS) of varying type, volume and purpose increased more and more.

An example of the most finished, technically perfect, and considered a model information retrieval system is the medical IRS "Medlars" created on the basis of the United States National Medical Library. Monthly information is fed into the machine's memory on each publication of 2300 biomedical journals.

Annually the supplement consists of about 200,000 articles and 16,000 monographs and books. With the help of this system the known bibliographic index is prepared, "Index Medicus" that includes 47% of the publications of the world medical periodical literature. This IRS can be used in the most diverse places of the United States through terminals (long-distance devices for the input and output of information in the computer) which have been installed in 10 medical libraries, 500 hospitals and institutes, and in a number of other institutions. Currently there are eight branches of the indicated "Medlars" system in operation in other countries (Australia, England, Canada, FRG, France, Sweden, WHO), and some of the branches themselves have become centers of scientific medical information for the service of other countries.

One of the world's largest centers of information in the field of science and technology is the All-Union Institute of Scientific and Technical Information (VINITI). The Institute processes about a million documents per year, among them 25,000 names of foreign and domestic journals, up to 20,000 books, and over 200,000 patent specifications. The automated information retrieval system "Assistent" which has been created in the VINITI every 2 weeks prepares several dozens of series of bulletins of current awareness information on different branches of knowledge, 70 annual issues of ITOGI NAUKI I TEKHNIKI, and every month puts out reference journals. The IRS "Assistent" is an irreplaceable help to the millions of scientists, engineers, and practical workers.

The director of the VINITI, Professor A. I. Mikhalov appearing at the Fourth All-Union Conference on Problems of the Development of a State System of Scientific and Technical Information stated the stages for the development of scientific and technical information in the country. The program of the CPSU and the decisions of the 24th and 25th Congresses of our Party provide for extensive introduction of the computer into different branches of the national economy, therefore at the first stage the all-union information organs will be transformed into automated centers of scientific information. At the second stage it is proposed to convert the branch territorial institutions into such centers. At the third stage a network will be formed of automated information systems connected with each other and with the broad network of subscriber's points. An exchange of data files on magnetic tapes will be organized between the systems.

The development of the service of scientific medical information in recent years, which is a component part of the all-state scientific and technical information system, is a clear testimony to the successful realization of the Party's decisions on this question. The All-Union Scientific Research Institute of Medical and Medical-Technical Information (VNIIMI) is the head institution in this service. The VNIIMI includes the State Central Scientific Medical Library, production-publishing kombinat (PIK), and the information and computer center (IVTs) on the basis of which the branch automated system of scientific information (OASNMI) is being developed. The OASNMI has been called upon to accelerate the process of medical information exchange in the country, and to increase the completeness and

efficiency of the information service to specialists of practical public health, NII [scientific research institutes], VUZes, the leading workers of the ministries of public health of the country and the republics, and the USSR Academy of Medical Sciences. This system is designed for automated collection, storage, retrieval, processing, output and transmission over a distance of medical information. The computer memory already holds about 100,000 units of information on problems: environmental protection, oncology, cardiovascular diseases, and demography. In addition data sub-systems have been created: scientific medical contents, biographies of Soviet and foreign medical scientists, scientific medical centers in the USSR and abroad, methods and equipment, chemicals and medicines, foreign trips of the country's medical scientists, and others. The OASNMI is being developed as a component of the automated control system "Zdravo-okhraneniye."

As the head institution the VNIIMI maintains a close relationship with the republic departments of scientific medical information (RONMI) in the country. At a definite stage in the development the automated system will communicate with the RONMI with the help of terminal devices or through computer centers of the republics. The vastness of the USSR territory, and the remoteness of the consumers from the central funds of the information sources requires the development and introduction of a communication system which would reduce to a minimum the times between request and response. Such a system of communication is the automated remote control communication system of OASNMI being developed in the VNIIMI. The RONMI of the Kirgiz SSR has been included in this system. In the course of a year 18 requests for copies of 165 articles and translations, and for 72 bibliographic collections were sent by teletype. The main customers were the NII of Health Resort Studies and Physiotherapy, the NII of Oncology and Radiology, the problem laboratory and TsNIL KGMI [central scientific research laboratory of the Kirgiz State Medical Institute], as well as certain departments. The time for obtaining a response, if the request is sent by teletype, is being reduced 3-4-fold. Experience has shown that such communication is especially effective for remote republics and cities.

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PUBLIC HEALTH

PROGRESS IN NEUROSURGERY DISCUSSED

Moscow NAUKA I ZHIZN' in Russian No 1, 1978 pp 30-32

[Article by A. Konovalov, corresponding member of the USSR Academy of Medical Sciences, director of the N.N. Burdenko Institute of Neurosurgery: The Scalpel and the Brain]

[Text] The object of study and neurosurgical intervention is the most perfect creation of nature, the human brain. Neurosurgeons who have at their disposal the most precise and perfect diagnostic methods possess unique potentialities for discovering the secrets of the brain's operation, and for helping it during diseases and injuries. From here follows the enormous importance of this branch of medicine for preserving human health. From here also follows the complexity of this science.

Neurosurgery was formed as an independent branch of medicine only under Soviet power. It was no accident that the great surgeon Nikolay Nilovich Burdenko wrote: "This science can rightfully be called Soviet." Until 1917 only individual Russian surgeons dared to operate on the brain. In vast Russia there was only one neurosurgical institution created by V. M. Bechterew and L. M. Pussepp.

If in other countries the evolution of medical disciplines, including neurosurgery, occurred and is occurring to a considerable degree spontaneously, and is mainly determined by the practical needs of today, then in our country neurosurgery was established from the first days of Soviet power for reasons of the plans and scientific substantiation inherent to the socialist structure.

In the USSR in the first place institutions were set up which could be the centers to guarantee the raising and solution of the most important scientific and organizational problems, and at the same time the training of neurosurgeons for the country. The scientific research institutes of neurosurgery in Leningrad, Moscow, and Kiev became precisely such centers. Here they developed according to the idea of N. N. Burdenko as complex institutions. Specialties bordering neurosurgery were included as organic elements. This principle of complexity was the basis for the building of neurosurgery as a discipline, determined the entire development of the Soviet school of neurosurgeons, and remains firm up till now.

Neurosurgery in our country, as by the way everywhere, began from neuro-traumatology. The great advances of this section of neurosurgery, and the efficiency of the developed treatment methods are primarily indicated by the experience of the Great Patriotic War when the life and health of many thousands of Soviet soldiers who had been seriously wounded were saved by the neurosurgeons. Then the beginnings were laid for the science of brain injuries. In the postwar period Soviet scientists obtained important data on the pathogenesis of trauma to the nervous system, and on the complicated diverse changes that occur in the entire organism during damage to the brain and spinal cord, and principles were developed for diagnosing and treating injuries to the nervous system and their consequences.

The evolution and formation of neurosurgery in our country has been constantly linked to the solution of another most important problem--treatment of brain tumors. The peculiarity of brain tumors is such that whatever their nature--benign or malignant--as they grow they inevitably, if surgical intervention is not undertaken, begin to squeeze the brain, and in the end the patient dies. Many major surgeons had an excellent understanding of this; as early as the end of the last and the beginning of our century they made daring attempts to remove such tumors on the basis only of data of neurological study in their judgements about where the tumor is developing. It is not surprising that the death rate during these operations was very high, and the cases of a favorable outcome were considered at that time as rare luck of the surgeon.

Now for the diagnosis of tumors and other brain injuries various diagnostic methods have been proposed which make it possible to determine the localization and nature of the process. Angiographic study has been highly perfected (x-ray contrast study of the cerebral vessels), in particular those of its modifications as selective angiography of individual vascular basins in the brain, pharmacoangiography (angiography with the administration of drugs), and so forth. More extensive use is being made in the neurosurgical clinic of brain scanning (use of radioactive isotopes to diagnose diseases).

A worthy place in this diagnostic complex is occupied by electrophysiological methods, and in the first place electroencephalography whose value significantly increases due to the use of methods of mathematical processing.

The technique of neurosurgical intervention has been considerably altered. More extensive use is being made of the so-called microsurgical method that makes it possible to preserve the most important brain structures even during the most complicated operations. These advances are especially impressive in the surgical treatment of benign tumors. Now it has become possible for radical removal of tumors located in the deepest and difficult to reach regions of the brain. Such operations, if they are performed in time prevent many extremely dangerous complications, and preserve vision.

The modern microsurgical technique makes it possible to remove from the tumor tissue the nerves exiting from the brain, the vessels supplying it with blood, and other important and easily injured formations.

At the same time for reliable treatment of all the intracerebral tumors it is necessary to solve still many complicated problems. Here one can count on success only after comprehending the biological laws for the development and growth of these tumors. Definite hopes are promised by the conducting of comprehensive treatment that includes surgery, irradiation, and the use of chemotherapy. Such studies are being done now in a number of our country's clinics.

In the number of new and more successfully solvable problems in the first place should be included treatment of vascular injuries of the brain. It is well known that these diseases are one of the most frequent causes of invalidism and death. Vascular injuries to the brain are diverse, and surgical intervention is far from used in all forms. But in certain diseases (for example, ruptures of aneurysms) this is the only possibility of saving the patient. Neurosurgeons in a number of major clinics in the Soviet Union are successfully performing complicated operations for these forms of injury to the cerebral vessels. Due to the extensive use of the microsurgical method the mortality rate for these operations has been reduced several times in recent years. It has become possible to remove aneurysms located in the deep regions of the brain. Soviet neurosurgeons have proposed original operations, and have developed the basically new, so-called endovasal method for treating a number of the most dangerous vascular injuries. This work was given the USSR State Prize for 1976.

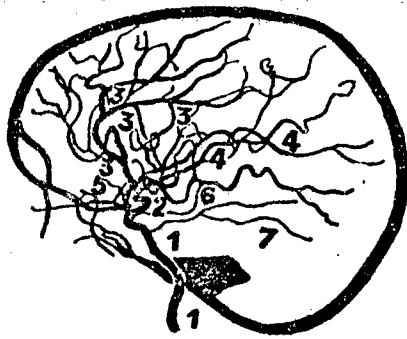
Such operations are most efficacious for vessels between the carotid artery and the cavernous sinus--diseases that are manifest as serious disorders in circulation and disruption of vision. The new method makes it possible to achieve normalization of blood flow, and to preserve the passability of the carotid artery, in other words-- to return the patient's health.

The research potentialities of this method are also enormous: by temporarily shutting off certain vessels of the brain one can study the most complicated processes of reconstruction of cerebral circulation, and the reaction of the brain to these changes in circulation. One can predict the outcome of the operation.

Neurosurgical operations are being successfully performed now also for certain forms of insult. It has become possible to perform reconstructive operations on the vessels of the brain itself as a result of which complete restoration of blood flow is attained.

The importance is ever increasing of the studies on rehabilitation of patients with different injuries to the nervous system, including those that have undergone neurosurgery.

The problems of treating the brain are so complicated that they can be solved only by the works of a broad front of specialists. Joint studies of scientists in different fields have provided a lot for a correct understanding of the problem of localization, the functions of the brain, for an explanation of the link between the cerebral structures and its functions, and for an interpretation and knowledge of the mechanisms of memory.



Angiography--method of x-ray study of blood vessels. Before photography or filming a harmless x-ray contrast substance is injected into the vessels which also develops them and makes them visible. Sometimes to avoid constriction of the vessels during examination vasodilators are injected into them. This method of diagnosis is called pharmacoangiography. The figure to the left illustrates the angiographic scheme of cerebral vessels. The numbers indicate the most important cerebral arteries. To the right--photoangiogram of the brain.

The progress of neurosurgery itself as a clinical discipline is unthinkable without basic research. Such research in the first place includes a comprehensive study of the problem of cerebral edema, a study of disorders in cerebral circulation and metabolic processes in the brain. Each year the front of these studies expands, and an ever greater number of neurosurgical clinics participate in them. Even now data have been obtained on changes in cerebral circulation after operations, and on how these changes can be corrected with the help of drugs. And these data are being successfully employed in daily practice.

But in rejoicing in the successes that our specialty has attained we are aware of how much still remains to be done. And we believe in the future of neurosurgery. We believe because we see how rapidly its potentialities are expanding due to the advances of the scientific and technical revolution. Only in recent years with the introduction of the so-called computerized axial tomography the diagnosis of cerebral diseases has been fundamentally altered. The human cranium has become as if transparent, and even the smallest changes in the brain's structure have been successfully seen through it. Moreover, attempts are already being made to transform these data into a three-dimensional holographic image. It is even difficult to imagine what perfection will be achieved by diagnostics in the next years.

The therapeutic potentialities of neurosurgery are expanding remarkably due to the use of the microsurgical method, new methods of radiation exposure (proton beam, stereotaxic introduction of radioactive isotopes) the use of ultrasound, laser, and others.

We believe in the excellent future of neurosurgery also because representatives of many specialties, including nonmedical, are deeply interested in studying the work of the human nervous system by those methods which neurosurgery has available.

Thus one can refer to one of the rapidly developing sections of neurosurgery, so-called functional neurosurgery which employs the methods of stimulation and local destruction of different links in the nervous system. These operations make it possible to make a deeper examination of the work of the nervous system, and are very important for biologists, biophysicists, and of course, neurophysiologists. The works of N. P. Bekhtereva, for example, indicate how these potentialities can be brilliantly employed.

In turn, certain studies of fundamental importance, for example, the investigation of the laws governing circulation and brain metabolism, are possible only with the unification of forces of neurosurgeons, physiologists, biochemists, pharmacologists, and other specialists.

The 25th CPSU Congress and the recent resolution of the CPSU Central Committee and the USSR Council of Ministers "On Measures for the Further Improvement in National Public Health" presented Soviet public health with tasks whose solution will promote to the greatest degree an improvement in the health of the Soviet people. We, the neurosurgeons, have an excellent understanding of the importance of these tasks and will do everything possible for their successful resolution.

All of us witnessed on what a scale the most important medical problems are solved in our country, and how the world's largest research complexes are created--oncological and cardiological. Evidently the time has come to create a research complex dedicated to comprehensive study of diseases of the human nervous system--"the brain center" in the direct and indirect sense of the word.

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PUBLIC HEALTH

APPLICATIONS OF MOLECULAR BIOLOGY TO AGRICULTURAL PROBLEMS

Moscow NAUKA I ZHIZN' in Russian No 1, 1978 pp 87-91

[Article by V. Soyer, head of the laboratory of molecular biology of plants of the Scientific Research Institute of Applied Molecular Biology and Genetics: Molecular Biology and the Bread of Tomorrow]

[Text] Molecular biology which was born in the middle of our century as a discipline that has, seemingly, a purely theoretical importance--knowledge of the bases of life, is already producing practical results. We have already written about many of them in this journal. This article only relates one applied "output" of molecular biology--acceleration of the selection work in the first stages of selecting new forms of agricultural plants.

Since time immemorial the selection of plants was that region of human activity in which intuition determined the success more than anything else. Growing of a new type took years or even decades, and the talented breeders, or originators, as they were often called, according to the one leading sign hybridized strains and selected new and better forms.

Despite the intuitive nature of their work the breeders of the past created masterpieces, often unsurpassed even today. Large-kernel Peruvian corn, the best strains of Central Asiatic melons and Russian apple trees (such as the antonovka), giant Japanese black radishes (weighing up to 15-17 kg), pumpkin, and many other examples characterized the work of the unknown breeders of the past. In displaying a real art in combining pairs for hybridizing and selecting the best form they brought selection to perfection, and even today almost a large part of the agricultural production man receives from strains either that remain unchanged since ancient times, or that have been created on the basis of the strains of the ancient selection.

The breeders of the past could not construct their work on anything else but the intuition which had been perfected: for until biology understood what heredity is, by what laws traits are transmitted from parents to progeny, and which intracellular structures carry the hereditary recording, the breeder had nothing else to rely on.

Only a little over 500 years ago the first information appeared in science of which genes determine the external signs of the plant organs. In the 1920's work was begun to compile the first genetic maps of plants. It became clear that such most important characteristics of the strain as resistance to viral and fungous diseases can be coded in the heredity. In 1925-1927 the possibility was discovered of artificial production of mutations, and the Soviet scientists geneticist L. N. Delone and breeder A. A. Sapegin, and the American researcher L. Stadler conducted the first tests to produce mutations in plants by radiation. Only as a result of these advances the first methods of experimental sciences began to penetrate selection.

This permitted the leading Soviet scientist Nikolay Ivanovich Vavilov as early as 1935 to advance the thesis that selection is ceasing to be an art and is becoming a science based on the achievements of genetics, cytology, and biochemistry. But since it is necessary in the creation of new strains to take into consideration a multitude of different aspects Vavilov stressed that "in contrast to the basic sciences like chemistry, physiology, botany, and zoology, selection as a scientific discipline is characterized by a high degree of complexity." Vavilov attempted to organize new scientific centers on plant selection in which side by side, in close unity, the breeders and phytopathologists, geneticists and cytologists, statisticians and biochemists would work. However decades were required before these ideas were realized on really broad scales in many countries of the world.

In 1969 at a dinner in honor of the Swedish and Soviet symposium of geneticists and breeders the leading Swedish scientist Oke Gustaffson, in returning to the idea of Vavilov that in the future selection must become a science, spoke with light humor: "Many, especially Americans, assure me that plant selection--this is an 'art,' and not a 'science.' Personally I have nothing against being called an artist, but as for plant selection, then I prefer to use the scientific approach." And here, in listing the tasks which the breeder is faced with today Gustaffson stated: "But how can the breeder today do his work if he is not capable of determining by an appropriate method the baking properties of a new strain of wheat? Or the brewing properties of barley? Or the composition of lipid acids in oil? Or the resistance of potato progeny to viruses or phytoflora? We have proved the importance of using the biochemical analysis of amino acids to improve corn, by isolating and then using mutants with a high content of lysine."

And only now, less than in a decade, it has become possible to use the biochemical and molecular-biological approaches in selection work.

Choosing the Initial Selection Forms

Success in creating a new strain begins to be determined even before the breeder conducts the first hybridization. Before hybridizing it is necessary to try as far as possible to get a more precise idea of the final result. And here the field for intuition was the widest. The breeders always sought an explanation by the best means of choosing the initial forms, but as the

task of accurate characterizing of the initial forms remained unrealized previously, so it remains unresolved to the end even today. In the textbooks on genetics and selection phrases are encountered on the important role of a number of methods of selection such as remote hybridization, use of geographically distant forms, selection of morphological variants, recurrent selection, and a multitude of others. However these are not so much the methods, as the principles of methods which can easily be explained theoretically, but are fairly difficult to apply in practice. It makes no difference if the travellers instead of a map with precise indication of the roads, the distances between the population areas and their population were simply given a clear picture.

Of course for breeders it would be most important first of all to learn to choose the necessary forms, even without sowing the seeds, and without waiting for the development of their plants, but by direct survey of the seeds or study of their properties in which the seed would not lose its germinating capacity. It is not difficult to understand that the development of these methods would be an advantage to breeders of herbaceous plants as the minimum of a year and of many years for those working on the derivation of new strains of trees.

But it is little to select the necessary forms for hybridization. Even more difficult tasks emerge after the hybridization has ended, the first seeds of the hybrids have been obtained, and now a minimum of 2 more years are needed in order to find out what the hybrids are, and what they have inherited from the father and what from the mother.

If the seeds of the first generation were successfully analyzed and the contribution of each of the parents in the formation of the hybrid seed revealed, the selection process would be accelerated a great deal.

Considerable progress in this field has been made in recent times. To illustrate these advances I will cite several examples of the most interesting, in my opinion, studies made in the last 2-3 years.

Electron Microscopy and Selection of Strains for Hybridization

Perhaps one of the exquisite approaches to solving this problem became the joint study of P. Pfaler from the Department of Agriculture of Florida University (United States), and G. Linskens and A. De Kok of the Department of Botany of Nymegen University (Holland).

Not long ago the stereoscan was created--an electron miracle microscope which made it possible to see a three-dimensional image of different surfaces--leaves, root hairs, skin epithelium. The obtained photographs opened a new world that was previously inaccessible to direct observation. This microscope was also used to study the peculiarities of the surface relief of 17 strains of corn. It was found that each of the strains has its individual "face" on the photograph, and by combining the tubercles on the surface of the seeds one could easily distinguish each of the strains just as through photographs of people the portrait similarities and differences are easily recognized.

However even more important was the fact that after hybridization of any of the 17 strains in pairs, by examining in the microscope the surface of the seeds of the hybrids a successful determination was made of which contribution in the formation of the hybrid was made by the paternal organism, and which by the maternal.

Differential Staining of Chromosomes

Another example in the same field is the use of a special method for staining the hereditary structures of the cell--the chromosomes in which the cross stria are revealed on them already in a standard light microscope. Their arrangement proved rather characteristic at least for different species of plants, and the experienced microscope user now can distinguish chromosomes of rye from chromosomes of wheat, and a number of other species.

The use of this method made it possible, for example, for D. Mettin of the M. Luther University in Halle (GDR) several years ago to discover a rather unexpected fact. It was found that in the creation by Academician P. P. Luk'yanenko of the remarkable strain of Caucasus wheat, half of a chromosome of rye had fallen into one of the wheat chromosomes. In the same way the use of the method of differential staining of chromosomes in a number of cases also could indicate to the breeder at the earliest stages of development of the hybrids which contribution in its formation was made by each of the parents.

Change in the Chemical Composition of Hybrids

Until very recently research did not cover the internal composition of hybrid cells to the extent that it is prone to analysis.

Works in this direction are now going full force. One should acknowledge as one of the most important results that fact that in each specific case the chemical composition of hybrids and their molecular filling is different. An important result in this sense was obtained by the Canadian scientists of Winnipeg University--D. Dexter and B. Dronzek. They analyzed the synthesis of different proteins in triticales, an intergeneric hybrid of wheat and rye which is now becoming more popular.

The researchers were not limited to single measurements, but traced the total content of protein and different protein functions in the maturing grain for the entire length of time of the development of the grain plants--from the moment of flowering to complete maturation. Here they discovered that the total number of protein molecules in triticales was closer to the wheat which was richer in protein, and the opinion could be formed that the hybrid mainly synthesizes its proteins according to the wheat type. However, when Dexter and Dronzek investigated which types of proteins comprise the summary proteins of triticales they could establish precisely that in content of different proteins (albumins, globulins, gliadins, glutenins, and insoluble

protein substances) the hybrid occupies an intermediate place between both parents. This intermediate nature was clearly visible also at the next, intramolecular level.

Proteins consist of amino acids, and the researchers decided to check the internal composition of the proteins of the hybrid. They were convinced that just as this was found in the relationship of the types of proteins, their internal amino acid composition was also intermediate in relation to both parents.

I repeat that one can now cite many examples of such research. Molecular-biological analysis is being used more and more to accelerate the initial stages of selection and to select the best forms. It is important that in the concept "best forms" now a basically new content is placed than 10 or 20 years ago. Previously the breeders were concerned mainly with external morphological traits--length of ear, number of kernels in it, height of plants, number of leaves, etc. Now the first place is occupied by factors of internal structure: protein content, content of lipids, amino acids, carbohydrates, and their balance, that which now it has been accepted to call the quality of the harvest.

Electrophoresis of Seed Proteins and Selection

Yet another field of molecular biological study that has become fairly developed in the Soviet Union has become important for the purposes of selection. This is the electrophoretic analysis of seed proteins of different strains of agricultural plants. Chemists long ago discovered that dissolved proteins placed in an electrical field begin to be moved until the actual charge of the protein molecules and certain other of their physical properties result in a stopping of this motion. Different proteins will migrate to a different distance, and by subjecting the mixture of proteins to scattering in a specific electrical field (electrophoresis--this is the name of this method) one can achieve separation of the mixture of proteins into individual components.

In 1959 the American researchers R. Jones, N. Taylor and F. Senti used the method of electrophoresis to analyze proteins of wheat grains dissolved in alcohol (they are called spars), and proved that these proteins are a mixture of molecules with varying electrophoretic mobility which will make it possible to determine their origin.

This method was greatly developed in the works of the laboratory directed by the corresponding member of VASKhNIL [V. I. Lenin All-Union Academy of Agricultural Sciences], Professor V. G. Konarev. This group succeeded in so improving the original method that it became possible to compile a catalogue of spectra by which one could determine without error what strain was being studied. Thus by using only an insignificant volume of alcohol infusion of the proteins (the content in it could reach several one hundred thousand or million parts of a gram) the scientists now should give a precise characterization of the strain.

The department of V. G. Konarev is included in the N. I. Vavilov All-Union Institute of Plant Growing in Leningrad--a world center that collects samples of plant seeds, and of course, the work of Konarev and his colleagues is enormously important for the specification of information on different strains in the world collection, determining the hereditary purity of material that newly enters the collection, and of solving many other questions that are important in the final analysis for the breeders of the whole world.

Another direction of the studies of electrophoresis of spare proteins of seeds of grain crops which also proved important for selection purposes was developed in Odessa--in the All-Union Selection and Genetic Institute, in the Department of Grain Quality headed by the director of this institute, corresponding member of VASKhNIL A. A. Sozinov.

In genetics it has been firmly established that each individual protein is synthesized under the control of a definite gene (in each chromosome several thousand genes can be arranged successively after each other).

This rule is correct also in respect to the spare proteins of grain crop seeds--wheat, rye, barley, oats.

The first question which the Odessa scientists were interested in concerned exactly the relationships of the genes of the spare proteins and the chromosomes. How are these genes arranged in the chromosomes? Do they all lie side by side, one after another in one chromosome, or are some genes of the spare proteins located in one chromosome, others in another, a third group in a third, etc.?

The scientists found forms of wheat in each of which one chromosome of their complete set was missing, and on the whole the entire discovered collection of mutants was a series, from which by selecting any one member and tracing its properties one could understand which genes had ceased to function due to the lack of a specific chromosome. In all the mutants the spectrum of proteins was studied in electrophoresis. Each protein produced a band on the electrophorogram, and on each such electrophorogram one could note several tens of bands. In standard studies each strain, variety, or mutant produced its spectrum of bands of spare proteins. Having employed this method the scientists found several important laws. First, it was discovered that the spare proteins are coded by genes of different chromosomes, and with a shortage of some chromosome a definite set of bands disappears from the spectrum. Second, by analyzing certain mutants a successful classification was made of the groups of protein bands on the electrophorograms, as if interconnecting the group of proteins and the corresponding chromosome.

Thus, the Odessa scientists extended the thread from genetics to molecular biology, and managed to reveal the link between protein molecules and genetic structures coding these proteins.

Came the second part of the experiment. Now the goal was set of using the attained information to solve purely selection tasks. This work, as said, was conducted in the Department of Grain Quality. The main task of the department--to study the technological properties of the obtained flour, and primarily its baking properties. However from an understanding of the fact that these qualities are completely determined by the properties of the protein molecules included in the grain composition to an explanation of definite traits by which the breeders could confidently select the lines of plants that combine in them a high yield and no less high technological qualities, is a distance of enormous size. One can even say that until today there are no such direct traits. The more valuable is the discovery made by A. A. Sozinov, F. A. Poperelya and colleagues of their laboratories. By analyzing the spectra of spare proteins in different mutants the Odessa scientists discovered that the presence of certain bands on the spectrum of proteins corresponds to the improved qualities of the flour. The researchers were convinced that in all the studied cases a successful prediction can be made beforehand in the new selection material of the necessary technological properties if one relies on the data of electrophoresis of proteins. It is easy to understand why this was so important for the purposes of accelerating selection.

In order to study the spectrum of proteins it was sufficient to "cut off" from the seed a small piece, and having obtained the electrophorogram to be convinced with one's own eyes if good progeny will be obtained from this grain or not. This operation did not interfere in the germinating capacity of the seeds, and 4-5 laboratory technicians could check thousands of samples in a week, and transfer for further testing a fortiori good material.

Thus still another thread was successfully extended--from genetics through molecular biology--to plant selection.

Cellular Enzymes and Resistance of Plants to Light Frosts

Investigation of the frost resistance of grain crops became an important task throughout the world. Each year in a certain region of the world winter crops die from freezing, and therefore both study of the causes of damage to crops by light frosts, and searches for winter-hardy plants acquire a more and more extensive nature.

One of the examples is the American scientist D. Kenefik who by artificially creating low temperatures traced how the plants will react to cold. It could be thought that those who are capable of more actively withstanding the cold endure better the minus temperatures. But what does withstand mean? Apparently, not to cease metabolism, that is synthesis of proteins, respiration, etc. Kenefik observed these processes in barley. However he found a completely different relationship.

It proved that the plants that do not withstand cold and die from it conduct active protein synthesis in their pre-death agony, while those plants which are capable of enduring the cold, on the contrary, as if die. The level

of the biosynthetic processes in them, and especially the level of protein synthesis was sharply reduced.

Having established this important relationship Kenefik decided to decipher the reasons for such behavior in the frost-resistant forms. In order to understand the course of his deductions we have to recall what determines the process of protein synthesis in the cells.

It has already been recalled that each protein is synthesized in the cells under the control of a certain gene. The synthesis occurs in several stages. From the gene, that is from the section of the molecule of DNA, its copy is read off in the form of a molecule of messenger RNA (m-RNA). This m-RNA is directed from the nucleus to the cellular cytoplasm where it is connected with special cellular structures ribosomes, and already the latter "are able to translate" the information written in the m-RNA into information on how the amino acids must be connected among themselves in order to obtain a protein chain corresponding to the given gene.

Why was the protein synthesis in cold in the frost-resistant forms of barley delayed? At what stage did the cell cease to synthesize proteins? Perhaps under these conditions the enzymes become inactive which make copies of the genes, or these copies themselves are unstable in frost? Or the frost impedes the ribosomes?

Having started to decipher this stratagem of causes and effects Kenefik discovered an important peculiarity of the cold-resistant forms of barley. Copies of genes in them were formed normally, that is synthesis of messenger RNA occurred the same as in the forms sensitive to cold. But these m-RNA did not make it to the ribosomes. In the barley cells resistant to cold special enzymes were formed, so-called ribonucleases, which destroyed the m-RNA molecules as soon as they were synthesized. Not receiving new matrices for protein synthesis the plants slowed down their metabolism, as if fell asleep, and in such a dormant condition survived the cold. At the same time in the barley forms not resistant to cold the necessary type of ribonuclease did not appear therefore the breakdown of m-RNA did not occur, and the overall metabolism, and in particular, protein synthesis, even increased in the cold. The plants rapidly spent their energy supplies and died.

Having explained the reason for the death of barley plants Kenefik switched to purely selection experiments. He requested from the selection stations located in all the states of the United States the most cold-resistant forms of barley. He checked their level of synthesis in cold of the corresponding ribonucleases, and by finding forms with active ribonucleases he made recommendations to the breeders for the most cold-resistant forms.

Growth Hormones and Dwarf Wheat

The green revolution was the name for the turnover in productivity of wheats that became possible due to the derivation in 1968 by the Mexican geneticist and breeder Norman Borlaog of new high-yield and semi-dwarf strains of wheats.

The Borlaog strain was distinguished by the ability to increase the yield the more fertilizer was placed on the field. This is a strain of the so-called intensive type. Borlaog--the only breeder to receive the Nobel Peace Prize as yet.

The second distinctive feature--giant ear on a short stalk. The nutrients synthesized by the plants are not expended for the growth of stalks, but mainly are moved into the ear. The dwarf nature of the wheat is the most important source of increased yield.

Long before the experiments of the Mexican scientist one officer in the British troops stationed in India found accidentally a short wheat and grew it at his house. This dwarf form Borlaog also used in his hybridizations with long-stalk strains.

The dwarf strains were not only used by Borlaog. In the USSR the leading breeder Academician Pavel Panteleymonovich Luk'yanenko also extensively used dwarfs, and created new strains of short wheat. And it is necessary to say that the Luk'yanenko strain, the same as the wheat of certain other Soviet breeders is not second to the yield of the Borlaog strains.

What processes on the molecular level characterize the dwarf plants? The physiologists in studying the growth mechanisms and development of plants discovered compounds which control these processes (by the way, it is apt to recall that the growth hormones were first discovered by the leading Russian scientist N. G. Kholodnyy). The growth hormones in an appropriate concentration can sharply intensify the processes of growth.

The biochemists joined the studies of the physiologists of plants. They were no longer interested in the final result--acceleration of growth and development, but in the molecular interpretation of this process. What is the stimulus for accelerated growth?

There were several such reasons; we will dwell on the important one. The most important factor that limits growth is the presence in the cells of available forms of such chemical compounds as simple sugars. The cell processes them from starch which as if serves as the storehouse for carbohydrates. But in order to convert starch (polysaccharide) into simple sugars special enzymes, amylases, are needed. These enzymes cut the massive molecules of polysaccharide-starch into the necessary short sections. Thus, the relationship is direct: the more amylase in the cell, the more it "exhausts" the simple sugars, and the more actively the accelerated development of the plantule occurs.

What determines the content of amylases in the cell? It was found that the quantity in the endosperm of the seeds of the copies of the gene that conducts the synthesis of the given enzyme is the determinant.

And the hormones, and in particular gibberellic acid, activate the work of the genes of amylase. In a unit of time the cell produces more copies from these genes in the form of molecules of m-RNA, and consequently, also synthesizes more molecules of amylase.

This discovery was also the basis for the use of gibberellic acid as the main tool in searching for dwarf forms. The colleagues of the agricultural research service in the United States G. Fik from North Carolina and K. Kvalset from the University of California at Davis found a simple method for selecting dwarf wheat at the level of the first plantules that appear from the seeds.

They sprayed the plantules with gibberellic acid. Those plants which had in the seed endosperm many copies of genes of amylases responded to this with an increase in the processing of the given enzyme. The plantules began to grow rapidly and to develop. While in the potential dwarfs with few copies of amylase genes in the seed endosperm--they grow was not intensified. It remains for the breeder to abandon the long "accelerants" and to work further only with the dwarfs. As we see the final result of these studies and the method proposed on their basis appear very simple. But the foundation of this simplicity--thousands and thousands of studies by scientists of varying specialties, large and small discoveries, and penetration into the depth of the treasures of the life processes.

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UDC 616.988.27

EPIZOOTIC CONDITION OF MOUNTAIN FOCI OF PLAGUE IN KIRGIZIYA

Frunze ZDRAVOOKHRANENIYE KIRGIZII in Russian No 2, 1978 pp 41-45

[Article by K.A. Aydraliyev and S.A. Berendyayev, Kirgiz Anti plague Station]

[Text] A systematic epizootological investigation of plague on the territory of Kirgiziya was begun in 1940, and already in the next year in Aksay infected marmots were found. During the next 10 years the main sites for the appearance of epizootic diseases were revealed which made it possible to determine the enzootic territory, to isolate in it regions with varying resistance and intensity of epizootic diseases, and to begin to sanitize the natural foci.

The main carriers of pathogen in the plague foci in Kirgiziya are gray and red marmots, while the lengthy keepers and transmitters of plague microbes are specific fleas of these animals. During epizootic diseases among the marmots sometimes other warm blooded animals infected with plague were found (narrow skull field mouse, gray hamster, light pole cat, fox, badger, and tolay hare) and certain Arthropoda (X-mites, lice from marmots, a number of species of fleas from narrow skull field mice). But these animals do not play an important role in the implanting of plague.

Marmots are widespread in Kirgiziya, but the plague foci occupy only part of their geographic range, mainly in the high mountain belt. Currently it is accepted to isolate two independent natural foci--the Tyan'-Shan' and Alay. The first of them is located along the crest of the Kokshaal, from Lake Chatyr-Kul' in the west to the upper part of the Sarydzhaz, and the area of 1.750 million ha occupied by them continues in Kazakhstan to the peak of the Khan-Tengri (the upper part of the river Tekes). The Alay natural foci occupies the eastern portion of a similar valley with the southern slopes of the Alay chain adjoining it. It also includes the area in the basin of the upper parts of the river Gul'chi from the pass Taldyk to the natural boundary Budalak. The area of the Alay foci is 200 thousand ha. Thus the enzootic plague territory is located in the mountain portion of the republic on an area of about 2 million ha.

The Tyan'Shan' natural focus of plague is broken up into autonomous foci which are named according to the main area of their location "Sarydzhaz," "Verkhnenarynskiy," and "Aksay." Until the marmots and their fleas were controlled this focus was active and stable until the marmots and their fleas were controlled. Beginning in 1941 the epizootic plague diseases were recorded annually, and the plague infected marmots comprised on the average for the focus about 0.6% of the number of those studied. The most active epizootic diseases occurred in the Dzhety-Oguzskiye watershed uplands in the natural boundaries "Uchkel'" and "Akshiyarak" (Verkhnenarynskiy autonomous focus) in which the infected marmots comprised respectively 1.5 and 1.2% (5,493 were studied). The least intensive epizootic diseases were recorded in central and west Aksay where up to 0.1% infected marmots were found (37,718 were studied), while on the remaining territory of Aksay there were about 1% infected marmots (32,186 were studied). In certain years on individual sections plague-infected marmots comprised a considerable portion of those studied: in 1958 in East Aksay--5.8%, in 1961 in Kuylyu--3.6%, and in 1964 Uchkul'--4.4%.

Stable and intensive epizootic diseases of plague and the constant threat of infection of people governed the need to sanitize the focus which was implemented by exterminating the marmots in Aksay and Sarydzhaz in 1955-1972, and controlling the marmot fleas (deep field disinfection of holes) in the Verkhnenarynskiy autonomous focus in 1971-1975. As a result a considerable reduction was attained in the epizootic activity of the focus and the danger of plague infection of people.

The Sarydzhaz autonomous focus was treated completely. Control of the marmots was completed in 1967. Further epizootological investigation was conducted here annually, and over 10,000 marmots and 32,000 ectoparasites were studied. As a result only in 1970 and 1971 two fleas were found infected with the plague pathogen. In 1972 on these sections local extermination of marmots was again conducted, and in the course of the last 4 years plague has not been found here. In 1974 in another place--in the natural boundary of Turuk after a 14 year interval plague epizootic disease was found and 8 strains of the plague microbe were isolated from marmots and their ectoparasites. In the next year this territory was treated by deep disinfection of holes and extermination of marmots. In the Aksay autonomous focus the struggle against marmots was conducted from 1955 through 1972. During this time extermination was implemented in an area of 700,000 ha. Only 50,000 ha were not treated in the natural boundary of Kurumduk, and this territory is currently epizootically active. Single extermination reduced the number of infected animals almost 20-fold in the East Aksay and South Aksay sections of the focus, while the periodicity of the manifestation of epizootic disease was reduced by 75% as compared to that of pretreatment. After a double, and in individual sections multiple extermination of infected marmots the infectiousness of the marmot of these sections was reduced 50-fold. If one takes into consideration also the significant reduction in the population of the marmots as compared to the initial density, then it is clear that the total saturation of the focus with the plague microbe was reduced 100-fold.

During the last six years (1971-1976) practically all the territory of Aksay was investigated. And certain epizootic sections which were more active in the past were investigated 2-3 times. About 20,000 marmots and other rodents, and 22,500 of their ectoparasites were studied. Thirteen cultures of the plague microbe were isolated from the marmots, including four strains obtained from two epizootic points in South Aksay, and one in East Aksay. In West Aksay in the basin of the river Terek in 1974 eight cultures of infection pathogen were isolated from six epizootic points. The result of the epizootological investigation indicate the presence of the plague pathogen in East and South Aksay, the activation of the epizootic disease among the marmots in the basin of the river Terak (West Aksay), which produces the need for further sanitation of this autonomous focus.

In the Verkhnenarynskiy autonomous focus extermination work was conducted with fleas of the marmots by means of deep dusting of the holes with a 10% DDT dust (field disinfection). From 1971 through 1975 550,000 ha of area was treated which is over 70% of the area of the focus. Until the sanitation plague epizootic disease in this focus was found annually, and the infected marmots on the average comprised 0.5% of those studied. In different regions this index fluctuates in the limits from 0.3% (in the Bolgartskiy section of the focus) to 1.5% (in Uchkel').

On the treated territory effectiveness of the field disinfection was established by epizootological investigation during the summer seasons of 1974-1976. The forces of the epidemic teams studied the plague infectiousness of 10,220 marmots and 2,163 other rodents and small ground predators, as well as 638 marmot fleas, 9,654 X-mites, and 7,077 lice collected from animals from their nests. The plague pathogen was not found. The good antiepidemic effectiveness was governed by a reduction in the population of fleas on the marmots and in their nests 50-100-fold.

The area in the basin of the river Uzengegush was not treated which is relatively isolated from the remaining territory of the focus by natural borders. The section was studied for four seasons and twice (in 1956 and 1975) intensive epizootic diseases were discovered. Thirty-one cultures of plague pathogen were isolated from marmots, and 22 strains from their ectoparasites. On the average according to the results of all the seasons of examination the infected marmots comprised over 1% of those studied.

In the Alay natural focus the plague pathogen for the first time was discovered in 1948. The epizootic territory consisted of 75,000 ha. It is located along the southern slope of the Alay chain between the passes Demey and Taumurun, and also occupies the natural boundary Kal'tabulak. Before the conducting of sanitation measures the territory of the focus was investigated. During 18 year seasons about 24,000 marmots and over 80,000 ectoparasites were studied. Plague epizootic diseases was found six times. Thirty-six cultures were isolated from the marmots (0.15% of the infected), 21 from their ectoparasites, and one strain from the badger.

In 1968-1970 for the purposes of sanitization on this territory extermination of marmots was conducted. Subsequently, in 1973 and 1976 during the epizootological investigation plague pathogen was not found. But in 1976 plague epizootic disease was found in the natural boundaries "Kalmaksu" and "Sary-Tash" located to the west from the border of the sanitized territory to the pass Khatyn-Art. on an area of about 10,000 ha. Eight cultures of the plague microbe were isolated from the marmots (1.8% of the infected animal) and four strains were isolated from fleas (three from Ceratophyllus lebedewi and one from Rhadinopsylla liventricosa). In this area there is the need to disinfect the holes of the marmots in order to suppress the epizootic disease and to prevent the danger of the plague pathogen spreading to the previously sanitized territory.

Many years of intensive epizootological investigation of the territories contiguous to and removed from the focus (here about 30,000 marmots were studied) did not produce positive results. Only in 1975-1976 was a new section of the focus revealed which was located along the northern slopes of the Alay ridge in the basin of the upper reaches of the river Gul'chi. According to the landscape-ecological signs it differs significantly from the epizootic territory of the high mountain region of the Alay focus. Both sections are connected by a system of passes through the Alay ridge, through which the settlements of marmots migrate from the northern slopes to the southern. During the two seasons of investigation from the Gul'chi section 2,033 marmots and over 40,000 of their ectoparasites were studied. Seventy-two cultures of the plague microbe were isolated. From the marmots 33 strains were isolated (1.6% of the infected animals), from the fleas C. lebedewi--30, from Pulex irritans--8, and from Oropsylla silantiewi--1. Epizootic disease was found in the following natural boundaries: Shart, Targalak, Askaly, Kichi-Bulolu, and Kunelek. The epizootic territory in the limits of the extreme points for the isolation of the plague pathogen consisted of about 25,000 ha.

It is necessary to draw attention to the isolation of the plague pathogen from the flea P. irritans which on this section in a large quantity are parasites on the marmots, although their main habitat is human residences. In 1975 the average summer index for P. irritans equalled 6.0 and consisted of 37% fleas collected from marmots. In 1976 these indices increased comprising respectively 11.3 and 51%.

The results of the serological methods of study are very indicative. In both seasons of investigation positive results were obtained in 13% of the marmots which were found both on the epizootic territory and in other natural boundaries--Taldyk, Archaty, Chon-Bulolu, Budalyk and Murdashi. The total area of the territory on which seropositive marmots were found consisted of about 100,000 ha.

The materials of epizootological investigation make it possible to conclude that in the Gul'chi section of the focus during the summer seasons of 1975 and 1976 intensive epizootic plague disease occurred among the red marmots. The main transmitters of the infection pathogen were the fleas C. lebedewi and P. irritans.

The epizootic territory is comparatively densely populated with people. Here over 15,000 people live continuously in 20 population points. The settlement Gul'cha, the rayon center, is located nearby. The automobile road Osh-Khorog and other roads pass over it, as well as paths on which the cattle breeders of Kirgiziya and Uzbekistan drive their cattle into the Alay valley for summer grazing.

Thus the epidemiological situation on this territory presents a great plague danger for people which requires intensification of the entire set of anti-epidemic measures the main of which must be epidemic observation, current field deep disinfestation of marmot holes (control of fleas), rat extermination and disinfestation in the population points, vaccination of people against plague, and extensive sanitary and educational work among the population.

Plague epizootic disease in Tyan'-Shan' and Alay has a clear seasonal cyclicity. The more than semi-annual dormant state of the marmots (September-March) determines the interruption in the epizootic process. In the active period of life of these animals the epizootic disease occurs more intensively in the summer season. The peak of its rise occurs in June-July. On the whole the entire focal territory the epizootic disease can continue up to four months (May-August). The greatest epidemiological danger occurs in summer when on the epizootic territory there are a large number of cattle breeders, and at the same time the marmot industry is being conducted.

In conclusion it should be noted that by now a sharp reduction has been achieved in the epizootic activity on a large area of the plague enzootic territory in Kirgiziya as a result of the extermination of marmots or the deep disinfestation of their holes (control of fleas). However the danger of people becoming infected is not excluded since on the sanitized section of the focus the marmot plague has not yet been successfully eliminated, and on the treated sections there remain active diseases especially in the Alay focus.

The population that lives continuously in the plague focus and those who live there temporarily must remember the safety measures in order not to catch the plague. The main means for human infection with the plague in Kirgiziya is direct contact with a marmot. This was proved by Dr. N. I. Tikhomirov as early as 1914 when for the first time he discovered the epizootic disease among marmots in Aksay and three cases of human plague, however the infection can also be transmitted by fleas. Due to this on the plague epizootic territory one must avoid contact with marmots and their holes. When dead marmots are found do not touch them with the hands but cover them with earth or stones. One should report their location to the antiplague epidemic team or to the nearest medical institution. All the population must be vaccinated against plague. In the population point it is necessary to conduct systematic rat extermination and disinfestation by all available means.

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UDC 616.981.42

ALLERGIC REACTIONS OF LEUKOCYTES IN CHRONIC BRUCELLOSIS

Frunze ZDRAVOOKHRANENIYE KIRGIZII in Russian No 2, 1978 pp 53-56

[Article by A.R. Dzhangaziyev, Department of Physiotherapy of the Kirgiz State Medical Institute]

[Text] The value of the infectious allergy in clinical brucellosis has been treated in detail by N. D. Beklemishev (1957, 1965, 1975). Almost all the clinical symptoms of the disease, including the injury of the vessels, and the nervous system have an allergic genesis. The degree of the allergic reconstruction during brucellosis has a great effect on the nature of the clinical course of the disease, and is one of the criteria for selecting methods of treatment.

Until present the degree of sensitization of the organism was judged according to the data of the Byurne skin test, but the skin allergic tests are associated with the introduction of a specific antigen into the organism which is not always indifferent for the organism. In addition skin sensitization sometimes can not coincide with the sensitization of the internal organs (N. D. Beklemishev, 1965), and does not always reflect the degree of allergic reconstruction of the organism.

Due to this in recent years more extensive use has been made of the allergic reactions of leukocytes that make it possible to diagnose the specific and nonspecific allergy outside the organism, i.e., in a test tube. Such reactions are indices for the damage to the neutrophils and agglomeration of leukocytes. They are widely used in tuberculosis, rheumatism, and bacterial and drug allergy.

The authors (R. G. Gudkova, 1967; M. I. Kitayev, 1972; and V. A. Fradkin, 1975) concluded that the reactions of deformation and agglomeration of leukocytes are more precise and sensitive as compared to the skin allergic tests.

The purpose of our work was to study the indices of these reactions in patients with chronic brucellosis, and the possibility of using them for diagnosis.

The reaction of neutrophil damage is based upon recording the amebiform activity of neutrophils during contact of blood with the corresponding

antigen (V. A. Fradkin, 1975). Alteration of leukocytes that begins after the reaction of the allergy with the antigen on the surface or near the cell is intensified by the active involvement of the leukocytes, in virtue of their general biological role, in the process of inactivation of the immune complex. In the cell the processes of metabolism are disrupted, which brings it to greater or lesser harm, thus disrupting the exchange of ions between the cell and the environment, disrupting the activity of cellular protease (N. G. Alibekova, 1975). The complement participates in the realization of this phenomenon (M. I. Kitayev, and I. B. Zasukhina, 1975).

The index of neutrophil damage during brucellosis was studied experimentally by Ye. A. Yel'chinova and M. D. Zhurb, A. N. Alibekova (1975), and in the clinic by Yu. V. Skavinskiy (1964), I. L. Kasatkina (1967), and A. S. Kugot (1975). The authors on the basis of the conducted studies concluded that this reaction is a reliable index for infectious allergy.

Another immunological phenomenon that reflects the presence in the organism of a specific allergy is the reaction of agglomeration of leukocytes (RAL) proposed by the Polish microbiologist L. Flek (1946). The basis for this was the fact of the tendency that he noticed for spontaneous agglomeration of leukocytes in uniform groups in a number of diseases. Bonding together of leukocytes increases with the addition to the blood of antigens that elicit sensitization (M. Ya. Kopylova, 1970).

The index of leukocyte agglomeration increases during tuberculosis (M. I. Kitayev, T. R. Ivakova, D. Kozhomkulov, 1972), during drug allergy (E. S. Tsatskina, 1974), but during brucellosis this reaction has not been studied.

We determined the reaction of agglomeration of leukocytes (RAL) and the indices for damaged neutrophils (IDN) with brucine.

The leukocyte agglomeration reaction was conducted according to the following technique. Two centrifuge test tubes were taken, in one of them 0.02 ml of 1.5% trilon-B salt were added in distilled water and 0.02 ml of 199 medium, and in the second tube the same amount of salt but instead of the medium 0.02 ml of brucine were added. Into both test tubes was added 0.04 ml of blood by a micro pipette. Then the test tubes were placed in an incubator at 37°C for two hours, after which smears were made from their contents (thick drop), they were dried and stained for one hour in a 0.01% solution of methylene blue. Under immersion the number of leukocytes bonded together into agglomerates were counted into groups of three or more cells, and according to diameter 500 bonded together and freely lying cells were counted.

The index of leukergy was determined according to the difference in the percent of bonded-together leukocytes in the test test tubes relative to the control to the total number of leukocytes counted.

Table 1. Reaction of Damage to Neutrophils and Agglomeration of Leukocytes in Brucellosis ($M \pm m$)

| (1) Контингент обследо- ванных | (2) Число обследо- ванных | (3) ППН | Р | (4) РАЛ | Р |
|---|------------------------------------|------------------|-------------|-----------------|-------------|
| (5) Здоровые | 32 | $0,01 \pm 0,001$ | — | $0,7 \pm 0,006$ | |
| (6) Привитые | 47 | $0,02 \pm 0,003$ | — | $1,7 \pm 0,4$ | |
| (7) Первично-хрониче- ский бруцеллез | 93 | $0,10 \pm 0,007$ | $P < 0,001$ | $6,4 \pm 0,5$ | $P < 0,001$ |
| (8) Вторично-хрониче- ский бруцеллез | 91 | $0,12 \pm 0,009$ | $P < 0,001$ | $8,8 \pm 1,3$ | $P < 0,001$ |
| (9) Рабочие мясокомби- ната | 37 | $0,10 \pm 0,01$ | $P < 0,05$ | $6,2 \pm 1,0$ | $P < 0,001$ |

Key:

- | | |
|-----------------------|----------------------------------|
| 1. Subjects | 7. Primary chronic brucellosis |
| 2. Number of subjects | 8. Secondary chronic brucellosis |
| 3. IDN | 9. Workers of meat packing plant |
| 4. RAL | |
| 5. Healthy | |
| 6. Innoculated | |

P--degree of reliability as compared to healthy.

Table 2. Reaction of Damage to Neutrophils and Agglomeration of Leukocytes in Patients with Chronic Brucellosis According to the Phase, Form, and Length of Disease

| (1) | Группы | (2) число обсле- дован- ных | (3) ППН | Р | (4) РАЛ | Р |
|-------------------------------------|---------------------|---|------------------|-------------|----------------|-------------|
| (5) | Здоровые | 32 | $0,01 \pm 0,001$ | | $0,7 \pm 0,08$ | |
| (6) Первично-хронический бруцеллез | | | | | | |
| (7) Фаза | Субкомпенсации (8) | 31 | $0,09 \pm 0,009$ | $P < 0,001$ | $4,8 \pm 0,6$ | $P < 0,001$ |
| | Компенсации (9) | 62 | $0,10 \pm 0,008$ | $P < 0,001$ | $7,6 \pm 0,7$ | $P < 0,001$ |
| | Смешанная (11) | 55 | $0,10 \pm 0,007$ | $P < 0,001$ | $6,9 \pm 0,7$ | $P < 0,001$ |
| (10) Форма | Периферическая (13) | 38 | $0,09 \pm 0,01$ | $P < 0,001$ | $5,7 \pm 1,02$ | $P < 0,001$ |
| (12) Длительность забол. | нервная система | 65 | $0,09 \pm 0,01$ | $P < 0,001$ | $6,7 \pm 0,7$ | $P < 0,001$ |
| | До 5 лет (14) | 28 | $0,09 \pm 0,009$ | $P < 0,001$ | $5,7 \pm 1,1$ | $P < 0,001$ |
| | Свыше 5 лет (15) | | | | | |
| (16) Вторично-хронический бруцеллез | | | | | | |
| (7) Фаза | Субкомпенсации (8) | 60 | $0,13 \pm 0,001$ | $P < 0,001$ | $7,4 \pm 1,2$ | $P < 0,001$ |
| | Компенсации (9) | 31 | $0,13 \pm 0,001$ | $P < 0,001$ | $8,7 \pm 1,2$ | $P < 0,001$ |
| (10) Форма | Смешанная (11) | 54 | $0,13 \pm 0,009$ | $P < 0,001$ | $8,5 \pm 0,8$ | $P < 0,001$ |
| (12) Длительность забол. | Периферическая (13) | 37 | $0,13 \pm 0,01$ | $P < 0,001$ | $6,1 \pm 0,2$ | $P < 0,001$ |
| | нервная система | 35 | $0,14 \pm 0,01$ | $P < 0,01$ | $6,2 \pm 1,6$ | $P < 0,001$ |
| | Свыше 5 лет (15) | 56 | $0,12 \pm 0,008$ | $P < 0,001$ | $5,8 \pm 0,7$ | $P < 0,001$ |

Key:

- | | |
|--------------------------------|-----------------------------------|
| 1. Groups | 9. Compensation |
| 2. Number of Subjects | 10. Form |
| 3. IDN | 11. Mixed |
| 4. RAL | 12. Length of disease |
| 5. Healthy | 13. Peripheral nervous system |
| 6. Primary chronic brucellosis | 14. Up to five years |
| 7. Phase | 15. Over five years |
| 8. Subcompensation | 16. Secondary chronic brucellosis |

P--degree of reliability as compared to healthy.

The reaction of neutrophil damage consisted of the mixing of 0.08 ml of blood with 0.02 ml of brucine in 5% sodium citrate. The same amount of blood and citrate was placed into the control test tube, but without the antigen. The reaction was conducted at a temperature of 37°C. After two hour incubation smears were made which were stained according to Shabadash with additional staining of the nuclei with hematoxylin. In each smear under immersion the condition of 100 neutrophils was determined. An evaluation of the effect in the test and control smears was conducted according to the amebiform reaction of neutrophils.

The index of damage to neutrophils (IDN) was determined by dividing the difference of the damaged neutrophils in the experiment relative to the control by 100.

There were 302 people under observation, of them 93 suffered from primary chronic brucellosis, and 91 from secondary chronic brucellosis according to the classification of N. D. Beklemishev. The indicated patients came under our observation with a confirmed diagnosis of chronic brucellosis.

In addition in order to judge the diagnostic value of data of the tests we investigated 47 people inoculated against brucellosis that did not have any complaints and did not have clinical symptoms of the disease, as well as 37 individuals (workers of a meat packing plant and other workers operating in animal husbandry) that had in anamnesis contact with cattle with brucellosis. The given category of examined patients had not been inoculated in the last five years due to positive serological reactions for brucellosis, but in the clinical status the presence of radiculitis, polyradiculitis or polyarthrititis was determined in the patient.

The studies revealed a statistically reliable increase in the indices of IDN and RAL with brucellosis in patients with chronic brucellosis, and in workers of the meat packing plant as compared to healthy individuals and those inoculated against brucellosis (Table 1).

Indices of the reactions in the examined individuals which had contact with cattle with brucellosis and in the clinical status had focal changes in the form of radiculitis, polyarthrititis, indicate that these people were infected with brucellosis, and the disease developed in them according to the primary chronic process.

It is apparent from Table 2 that the indices for both reactions are higher in patients both with primary and with secondary chronic brucellosis in the mixed form of the disease where there is simultaneous infection of the peripheral nervous system and joints as compared to the data for those patients in which only the peripheral nervous system is involved in the process.

The increase in the IDN and RAL occurs in the same way in patients with length of disease up to five years, especially in secondary chronic brucellosis which indicates the more pronounced sensitization of the organism and the activity of the process in the first years of the disease.

Thus the obtained data make it possible to assert that in chronic brucellosis the allergy touches the leukocytic elements of the blood and that the aforementioned tests with brucine can be used to reveal the autosensitization of the organism.

The simplicity of establishing the reactions for damage to neutrophils and agglomeration of leukocytes makes it possible to recommend their use under conditions of any clinical laboratory; these reactions in the presence of clinical data and accompanying epidemiological anamnesis can have auxiliary importance for diagnosing chronic, especially primary chronic brucellosis.

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UDC 614.2

CERTAIN DEFECTS IN MEDICAL AID ACCORDING TO THE DATA OF THE EXPERT PRACTICE OF THE REPUBLIC BUREAU OF THE FORENSIC MEDICAL COMMISSION OF EXPERTS OF THE KIRGIZ SSR MINISTRY OF PUBLIC HEALTH

Frunze ZDRAVOOKHRANENIYE KIRGIZII in Russian No 2; 1978 pp 56-58

[Article by G. M. Sirotkin, B. M. Semenov and L. N. Koverga, Republic Bureau of the Forensic Medical Commission of Experts of the Kirgiz SSR Ministry of Public Health]

[Text] It is generally known that the rendering of timely and qualified medical aid to the population depends to a great extent on the clear organization of work in different links of the system of the public health organs.

The increasing demands for the quality of medical aid to the population place on the agenda the task of a systematic analysis of defects in rendering medical aid. In the specialized literature materials are periodically published of the opinions of experts on "medical cases" (Yu. S. Zal'munin, 1950; Yu. P. Edel', 1957; G. A. Galil-Ogly, 1957; G. S. Noreyko, 1963; Yu. F. Ogarkov, 1961, 1966; A. P. Gromov, 1969; A. B. Michkov, 1972, and others).

The most acutely felt are defects in the activity of the medical workers; due to this the emergence of each "medical case" is considered an emergency event. Analysis of the reasons for the occurrence of errors, and elimination of the deficiencies in the work are one of the effective means of improving medical and preventive aid to the population.

We made an analysis of the opinions of experts for the last 5 years for cases raised by the organs of investigation in relation to the medical workers for complaints of the relatives of the deceased, or on the initiative of the investigative organs themselves. Of definite interest were the materials of 30 criminal cases. Accusations of careless and negligent attitude towards service duties, and insufficient attention to the patients mainly concerned surgical specialists (16 cases); roughly the same percentage--therapists and gynecologists. The remaining cases concerned physicians of other specialities.

With the permission of the expert commissions, that included the leading specialists of the Kirgiz SSR Ministry of Public Health, the heads of the departments of the KGMI [medical institute], and experienced forensic medical experts, a definite range of questions was raised of which the main were the correctness of the clinical diagnosis made and the treatment given; the timeliness and completeness of the medical aid; the correspondence of the treatment measures to the appropriate instructions, statutes, orders, etc.

The materials of four commissions of experts were the subject of further forensic examination, and the guilty parties were punished in a criminal order. In 26 cases in the process of inquiry, on the basis of objective and scientifically justified conclusions of the expert commissions the charges were removed from the medical personnel, and the criminal cases raised were stopped due to the lack of a crime.

Analysis of the experts' opinions indicated that the main defects in the work should include careless formation of the medical documents; insufficiently complete explanation of anamnesis of the disease; very laconic recording of the objective symptoms of the sickness and the volume of operational interference; irrational medicinal therapy, and so forth.

The physicians of the medical institutions of the republic at times, unfortunately, forget that the chart of the hospital and out-patient patient is the main judicial document, and has legal importance in establishing the guilt or innocence of the medical worker.

Often when the expert's opinion was made it was difficult to determine the degree of violation by the physician (or another medical worker) of the service duties.

Negligence in service duties is included in the crimes provided for in article 179 of the "Criminal Code of the Kirgiz SSR," in which by negligence is meant: "...nonfulfillment or excessive fulfillment by an official of his official duties as a consequence of careless or unconscientious attitude towards them that causes significant harm to the state or public interests, or to the rights and interests of individual citizens that are protected by law."

The law does not define the list of specific actions included in the concept of undue and careless attitude in the physician's activity.

Judicial practice mainly means by such actions: 1) insufficient examination of the patient; 2) careless use of drugs; 3) late or lack of hospitalization of the patient; 4) violation of the established instructions and rule for treating and examining a patient; 5) carelessness in performing operations; 6) careless treatment of patient.

As an example of negligent fulfillment of service duties one can cite the following from investigative practice:

10 October 1974 citizen B, 13 years old, entered the Groznyy district hospital of the Kirov rayon for medical aid because of a fractured right radius in a typical place. Having examined the patient the physician on duty, a therapist, applied a rear gypsum dressing and recommended to the patient's parents that they see a surgeon which they did the next day. Surgeon O., having examined the patient, did not pay attention to his complaints of intolerable pains in the limbs, and a feeling of numbness in the fingers, and sent the patient home. 14 October 1974 the parents again came to the surgeon with the boy and said that the boy does not sleep, tosses from pain, and some kind of blisters had appeared on the wrist. Surgeon I. lanced the blisters and sent the patient home without checking the condition of the dressing. 22 October 1974 the upper right limb of patient B. was amputated to the level of the middle third of the shoulder as a consequence of gangrene.

At the complaint of the relatives a suit was filed and surgeon O. was condemned by verdict of the people's court.

In individual cases the reasons for the development of unjustified "medical cases" were related to the fact that the patients did not know the potentialities of medicine, or were governed by a belief in its power for any disease and any injury. In a number of cases the reason for the suit, unfortunately, was the inobservance of medical ethics, and incorrect attitude towards the relatives of the patients and the deceased, as well as incorrect information on the nature of the disease and the cause of death obtained from the middle or junior medical personnel.

The following example can indicate crude violation of the moral and ethical norms. In one of the hospitals in Frunze patient D. suddenly died during the administration of a drug. This patient was soon to be released from the hospital because of an improved health condition and the stability of remission. When the husband of the deceased came for his wife on the day of release he was told rather crudely: "You can do nothing here, your wife has died."

Naturally after such an "explanation" a completely justified complaint was filed for incorrect treatment.

It is our deep conviction that systematic analysis of the defects in medical aid and the causes of medical errors can promote an improvement in the quality of medical aid to the population, and can reduce the number of unjustified occurrences of so-called "medical cases."

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PUBLIC HEALTH

CURRENT STATUS AND PROSPECTS OF DEVELOPMENT OF MEDICAL SCIENCE IN TURKMEN SSR

Ashkhabad ZDRAVOOKHRANENIYE TURKMENISTANA in Russian No 11, 1977 pp 21-27

[Article by K. Sh. Shagylydzhov]

[Text] The Soviet state, whose 60th anniversary is being celebrated this year by all of progressive mankind, devoted, from the very beginning, much attention to development of public health care and medical science. Scientific medicine was virtually nonexistent in Turkmenistan before Soviet power was established.

At the present time, within the system of the TSSR [Turkmen SST], the Turkmen State Medical institute and several scientific research institutes, which are constantly being reinforced with scientific personnel and a material and technical base, are functioning with success. The substantial changes that occurred in this respect are referable to the last 10-15 years. While there were 9 doctors and 1003 candidates of medical science working in scientific institutions in 1964 (I. F. Berezin, 1964), there were 516 scientific workers in 1976, including 25 doctors and 238 candidates of medical science. In addition, many practicing physicians (including 65 candidates of medical science) are involved in scientific research, and they are allied in republic-level and oblast scientific medical societies. At the present time the scientific medical men of Turkmenistan are capable of solving not only local scientific problems, but those of All-Union and international significance. However, this was not always the case.

In the late 1920's and early 1930's, 7 scientific medical institutions were organized in Turkmenistan, including the Turkmen State Medical Institute.

In 1927, the Institute of Neurology and Physical Therapeutic Methods was founded (presently the Turkmen Scientific Research Institute of Neurology and Physiotherapy); the Institute of Social Hygiene (presently chair of social hygiene and public health of the TGMI [Turkmen State Medical Institute]) was founded in 192; the Institute of Microbiology and Epidemiology (presently called the Ashkhabad Scientific Research Institute of Epidemiology and Hygiene) was opened in 1929; in 1932, four institutes were founded at one time: the Turkmen Scientific Research Institute of Trachoma (presently the Turkmen Scientific Research Institute of Eye Diseases), Turkmen Scientific

Research Institute of Dermatovenereological Diseases (presently the Turkmen Scientific Research Institute of Skin Diseases), Turkmen Scientific Research Institute of Tropical Diseases (presently merged with the Ashkhabad Scientific Research Institute of Epidemiology and Hygiene), and Turkmen State Medical Institute. Later on, in the early 1960's, two more scientific research institutes were founded (Turkmen Scientific Research Institute of Tuberculosis in 1962, and Turkmen Scientific Research Institute of Oncology in 1963).

Because of the establishment of the scientific research institutes, and particularly the medical institute, the government of TSSR invited medical scientists to work here, from other republics, mainly from the Russian Federation; they played their role in the inception and development of medical science in Turkmenistan. The following were among these scientists: A. V. Parabuchev, pathoanatomist; O. Ya. Rezhbek, histologist; Ya. V. Rezhbek, hygienist; V. A. Dzikovskiy, pharmacologist; A. F. Samoylov, chemist; V. P. Sokolov and V. F. Dedushenko, physicists; K. I. Tsukulenko, ophthalmologist; N. A. Kevdin, internist; D. P. Kirika and S. S. Danilov, anatomists; D. P. Livanov, gynecologist; A. I. Venchikov, physiologist; S. N. Strukov, specialist in forensic medicine; A. V. Vinogradov, biologist; V. D. Timakov, epidemiologist; V. S. Suknev, microbiologist; I. V. Grigor'yev, surgeon; A. P. Lavrov, dermatovenereologist, and others.

Some of the scientists who participated actively in organizing and developing medicine in Turkmenistan are still working with success at the TGMI. We refer to professors O. Ya. Rezhbek and A. I. Venchikov, and Docent V. F. Dudushenko.

The scientific medical institutions of the TSSR Ministry of Health, which were strengthened with respect to organizational aspects in the 1930's, undertook work on the most pressing problems of public health in this republic, such as control of ophthalmological, infectious, dermatovenereal and other diseases, and accomplished remarkable results in these areas.

The TGMI is the largest, it is adequately manned by scientific personnel and for this reason it is the leading scientific medical institution in the republic. Scientific research is being conducted on all chairs of TGMI, including therapeutic. From the very start, the medical scientists of Turkmenistan concentrated on the problem of cardiovascular pathology, as related to the hot climate of our republic. As far back as the 1930's, the work of Prof N. A. Kevdin dealt with functional diagnostics of cardiac pathology. Subsequently, there was comprehensive scientific development of cardiovascular pathology. The clinical aspects of etiology, pathogenesis, diagnostics and therapy of cardiovascular diseases were worked on by professors G. A. Kazimov and A. Ch. Charyyev, docents A. K. Vavilkina, S. A. Radyukova, R. Zakhar'yants, S. Ch. Berkeliyeva, A. Mamedkuliyeve, B. A. Atayev and others. Problems of surgical diagnostics and therapy of these diseases, in particular, congenital heart disease, were reflected in the works of professors N. M. Tachmuradov and K. K. Kurdov, A. Yevzhanov, candidate of medical sciences, and others.

Docent O. M. Karryyev offered a sociohygienic evaluation of conditions under which cardiovascular diseases occur among the inhabitants of our republic. The research of Prof K. Shaglyldzhov and A. A. Orlova, candidate of medical sciences, dealt with the problem of sudden death due to acute cardiac ischemia. Problems of pathomorphology of atherosclerosis, essential hypertension and myocardial infarction were worked on by professors O. Ya. Rezhbek, E. E. Kenig and Sh. M. Karimov, as well as T. B. Babadzhanova and K. A. Khalnazarov, candidates of medical sciences.

At the present time, all of the scientific research dealing with cardiovascular pathology is being coordinated by a problem commission bearing the same name under the supervision of Prof G. A. Kazimov.

Research on gastroenterological diseases, which was begun by Prof B. L. Levin, was continued by professors S. L. Gaukhman and G. K. Khodzhakuliyev, and docents M. M. Mamedova and M. A. Pishchayeva.

The main directions of research were problems of hepatic pathology (Prof S. L. Gaukhman), treatment of gastrointestinal diseases with "chal," a sour camel milk product (Prof G. K. Khozhakuliyev) and investigation of therapeutic properties of camel's thorn broth, as well as clinical application thereof (N. A. Sinel'nikov, G. E. Shasuvarov and others). The study of endocrinological diseases, begun by professors A. T. Sukachev and I. V. Grigor'yev, is presently being continued by docent D. M. Allberdyev.

At the present time, problems of cardiovascular pathology, gastroenterology, pulmonology and endocrinology are, as before, the main scientific directions of therapeutic disciplines.

Research on the surgical chairs of TGMI was devoted to the most diverse problems of this multifaceted discipline. Thus, Prof M. I. Mostkov and B. Kh. Khanov, candidate of medical sciences, investigated osteomyelitis and intraarterial administration of drugs; work on treatment of diseases of the skeletomuscular system, begun by Prof D. M. Labok, is being successfully continued by docent O. A. Mavyev and his colleagues; scientific research on the pathogenesis and treatment of traumatic shock was the main direction in the creative activities of Prof N. M. Tachmuradov and his colleagues; many scientists, under the guidance of Prof Ch. B. Bayriyev, are working well on the problem of using ozocerite [fossil wax] in surgery. Prof I. F. Berezin and his colleagues worked on surgical management of cancer and prolapse of the rectum; Prof D. Ya. Khalikov developed problems of treatment of pathology of the esophagus; Prof O. G. Babayev was concerned with surgical management of parasitic diseases, particularly amebiasis of the liver; docents V. N. Sergeyeva, M. Kh. Dovlekamov and N. I. Tarasov researched urolithiasis; docent P. N. Nurmedov and E. Saklapov, candidate of medical sciences, investigated fluid-electrolyte metabolism in the presence of surgical pathology; docent B. S. Soltanov worked on surgical tactics and methods of treatment of wounds to chest organs in peacetime.

Considerable research was conducted by representatives of narrow surgical specialties: pathology of the ear, nose and throat (docents B. Kh. Khydyrov, M. Atamuradov, G. N. Vasil'yev and others) and stomatological diseases (Prof V. V. Dadal'yan; P. K. Tanrykuliyeu, doctor of medical sciences; docent K. P. Pashayev and others).

Representatives of surgical disciplines were the most active in such an important area of research as introduction of scientific advances in public health practice. In the last 3 years, docent O. A. Mavyev et al. developed and introduced 25 rationalization proposals, while docent Yu. M. Volobuyev et al. offered more than 30 rationalization proposals.

The chairs of obstetrics and gynecology, pediatric faculty and chair of pediatrics on the medical faculty are involved with scientific problems of mother and child care.

The main directions of scientific research dealing with obstetrics and gynecology are referable to questions of obstetrics (Prof D. P. Livanov), vascular permeability in the presence of obstetric pathology (Prof A. B. Preysman), obstetric hemorrhages in a hot climate (Prof K. M. Bazhenova), ozocerite therapy and treatment at the Archman resort of inflammatory diseases of female reproductive organs (docents M. S. Seyradov and V. L. Yufarkin).

Docent I. D. Der'yayev conducted much research on the level of physical development of children in TSSR. In addition, studies are in progress on chairs of pediatrics, which deal with pneumonia (docent Ya. S. Sakhatov et al.) and rheumatism in children (docent A. F. Sergiyenko).

Much is being done at the TGMI in the area of theoretical medicine. Prof A. I. Venchikov is one of the veterans of Turkmen medical science; his scientific interests cover a wide range of problems: electrophysiology of the stomach, climate-related physiology (fluid intake in hot climates), trace elements and therapeutic use of biotic agents.

Pathophysiologists, headed by Prof V. A. Yusin, made a significant scientific contribution to the study of metabolism in the presence of tropical avitaminosis, effects of snake venom on the body (A. T. Berdyeva), vascular permeability (A. G. Anna-Gel'dyeva, F. F. Sultanov, I. I. Todris). In the last few years, Prof A. K. Anna-Gel'dyeva and her colleagues have been studying the incidence of leukemia in Turkmenistan and pathophysiology of poisoning due to toxic chemicals.

Considerable work was done on the study of changes in metabolism, correlation between viscera (stomach and kidneys), drug and resort resources of the republic (Turkmen juniper, Archman, Ashkhabad and Farab mineral water) by the staff of the chair of pharmacology (T. I. Kazachkova, N. M. Annamuradov, M. N. Krylova, T. G. Khodzhael'dyev, N. M. Mollayev) under the supervision of Prof V. A. Dzikovskiy.

The staff of the chair of biology, under the supervision of Prof A. V. Vinogradov, investigated the medicinal flora of TSSR and phytoncidal properties of some plants. Later on, the same personnel dealt with problems of endemic diseases (docent G.A. Pravikov). At the present time, investigation of hereditary diseases of man (A. T. Berdyeva, doctor of medical sciences; B. Babayev, candidate of medical sciences) is the main research direction on this chair.

The research work done by the staff of the chair of medical chemistry has much in common with the problems being developed on physiological chairs. In particular, Prof A. F. Samoylov is concerned with the vitamins of the flora of TSSR; Prof V. I. Sergiyenko and docent R. N. Karimova are studying the influence of balneological factors of TSSR on metabolism. The research of Prof F. F. Soprunov, A. Kh. Babayeva, doctor of medical sciences, and docent Kh. K. Kurbanova deals with synthesis of proteins.

Docent Kh. K. Kurbanov and his colleagues are presently working on biochemistry of melaninogenesis.

Much scientific research is being done on chairs of morphological disciplines. The main directions of scientific research on the chair of normal anatomy were and still are problems of angiology. Work on the state of the vascular system of the skeletomuscular apparatus is being conducted under the guidance of Prof S. S. Danilov (D. Khudayberdyev, L. P. Katunina, A. Yu. Markhuda, M. M. Lysenko, T. A. Kafiyeva and others). Prof S. Z. Rosenman and his colleagues are studying variability of the vascular system of internal organs under various exogenous and endogenous conditions.

Problems of angiology were also investigated by many of the staff members on the chair of topographic anatomy (docent G. A. Ikonnikova, T. I. Berezina, S. S. Remennik and others). At the present time, this chair, under the supervision of docent G. A. Amanov, is working on surgical topography of the pancreas.

The scientific research pursued by the staff of the chair of pathological anatomy, under the supervision of one of the founders of TGMI, the most prominent scientist and organizer of medical science in our republic, Prof A. F. Parabuchev, was multifaceted and fruitful. They worked on the distinctions of pathomorphological processes associated with various specific infections--tuberculosis, brucellosis and others (A. V. Zhukhin, Ye. A. Gratsianskaya). In the last 25 years, the scientific work on this chair, under the supervision of Prof O. Ya. Rezhbek, dealt with pathomorphology of cutaneous leishmaniasis (Sh. M. Karimov, Ye. A. Gratsianskaya), pathological anatomy of the plague (E. E. Kenig), endocrine pathology (K. A. Khalnazarov, Ya. P. Pirlekov, F. A. Nezamov) and pathomorphology of poisoning by toxic chemicals (O. Ya. Rezhbek, K. A. Khalnazarov, T. V. Babadzhanova).

The staff of the chair of forensic medicine (S. N. Strukov, K. Sh. Shaglyldzhov, A. A. Orlova and others) were also concerned with problems of toxicology.

For the public health service of our republics, control of infectious diseases, improvement of the epidemiological situation and hygienic conditions were among the pressing tasks. The main direction of research in this area was development of measures to eradicate epidemic and parasitic diseases (V. V. Suknev, V. D. Timakov, V. A. Friauf, M. I. Bogdanovich and others) and malaria (Ye. N. Pavlovskiy, P. A. Petrishcheva, G. N. Pravikov).

Problems of epidemiology, hygiene, treatment and prevention of infectious diseases are being worked on by the Ashkhabad Institute of Epidemiology and Hygiene imeni S. M. Dursunova (director, B. Kh. Bagirov, doctor of medical sciences), the staff on the chairs of hygiene (headed by docent A. A. Nepesov), microbiology (headed by docent Ye. G. Stepanyan) and infectious diseases at TGMI (headed by docent N. E. Esenov). The range of scientific topics that epidemiologists, hygienists, microbiologists and infectious disease specialists are working on were and remain diversified. The main ones are: problems of intestinal diseases (Prof V. D. Timakov, docent A. V. Vasil'yeva, K. A. Shaferova and others), stages of development of spirochetes of relapsing fever (Prof V. A. Skavinskiy), water supply hygiene (Prof M. I. Sergeyev), hygiene of nutrition (docent K. A. Kuliyeu), industrial hygiene referable to oilmen and builders in hot climates (B. Kh. Bagirov, doctor of medical sciences), industrial hygiene for school children (Kh. I. Kuliyeu), epidemiology of leishmaniasis (S. M. Dursunova, doctor of medical sciences; M. Belova and Ye. N. Ponirovskiy, candidates of medical sciences), clinical and virological studies of epidemic hepatitis (docent N. E. Esenov, N. V. Kiseleva, N. M. Nepesova), microbiology of salmonellosis (docent Ye. G. Stepanyan).

Trachoma follows infectious diseases as the bane of the Turkmen people; organization of the control thereof was assigned to the Trachoma Institute (presently called the Turkmen Scientific Research Institute of Eye Diseases). The main scientific problem for the institute and chair of eye diseases of TGMI was to investigate the incidence and organize control of trachoma and other diseases of the eyes. K. I. Tsykulenko, N. M. Pavlov, S. A. Barkhash, S. M. Shchupak, M. S. Mertslin and others were the organizers and first scientific workers at the institute.

Scientific work on methodological and organizational measures for the control of trachoma, pursued under the supervision of Prof S. K. Karanov, was completed successfully and, in the mid 1960's, trachoma was totally eradicated from our republic.

At the present time, the staff of the Turkmen Scientific Research Institute of Eye Diseases (director, Kh. Ch. Annaredzhapov, candidate of medical sciences) and the specialized chair of TGMI (headed by Prof S. K. Karanov) continue to investigate diagnostics, treatment and prevention of the most prominent eye diseases: glaucoma, ophthalmomycosis, viral and allergic pathology of the eyes, protection of children's sight (Prof N. N. Nurmamedov, docent Z. K. Beknazarova, R. L. Grigor'yants; Kh. Shukurov, candidate of medical sciences; A. B. Berdyev, B. B. Berdyev, S. K. Charyev, N. N.

Maksimenko, L. N. Tarasova, A. N. Afanas'yeva and others). Scientific advances are being actively introduced at the institute to public health practice. Much work was done, under the supervision of Prov N. N. Nurmamedov, for the development of microsurgery of eye diseases.

The Institute of Neurology and Physiotherapy (director, N. M. Annamuradov, candidate of medical sciences) is one of the oldest scientific research institutes of the TSSR Ministry of Health. The main direction of research conducted at this institute is the study of neuropsychiatric diseases, endocrine gland and metabolic pathology, diseases of the skeletomuscular system and development of physiotherapeutic and balneological-climatological treatment methods. These problems are also being investigated by the staff of the chairs of nervous diseases (headed by docent K. O. Orazov), physiotherapy and therapeutic physical culture (headed by M. G. Berdyklychev, corresponding member of the TSSR Academy of Sciences) and, to some extent, the chair of psychiatry (headed by docent L. S. Ladygina) and several other clinical chairs.

Prof B. L. Smirnov, academician of the Turkmen Academy of Sciences, deserves much credit in the inception and development of scientific research; under his supervision, work was done on the study of resort factors in the republic, neurobrucellosis (Prof Ye. I. Tarakanov, M. A. Lysenko) and neuroendocrinology (Prof I. L. Skobskiy). Prof B. L. Smirnov is the founder of neurosurgical care in our republic; his work is being continued with success by docent Yu. M. Volobuyev, on the chair of nervous diseases.

More recently, research at the institute and specialized chairs of TGMI has dealt with further investigation of resort and climatological factors in the republic (N. M. Annamuradov, V. A. Krivonogov [deceased], A. F. Febraleva, D. M. Allaberdyev, I. G. Oksenich and others). Studies are being pursued of problems of treatment and rehabilitation of patients with acute and chronic cerebrovascular disorders (M. A. Lysenko, V. A. Krivonog, N. I. Nikolayeva and others).

With regard to development of the scientific bases of dermatovenereology in Turkmen, much work of an organizational and research nature was pursued by the staff of the Institute of Skin Diseases and chair of skin diseases at TGMI, under the scientific guidance of Prof N. F. Rodyakin. Development of measures for the control and eradication of skin and venereal diseases in the republic is the main scientific objective of the institute and chair.

The main directions of scientific research at the institute are referable to treatment, prevention of dermal leishmaniasis (P. V. Kozhevnikov, I. I. Gitel'man, N. F. Rodyakin, M. E. Ereshov, R. S. Dobrzhanskaya, Ye. M. Belova, N. M. Khanmamedov and others) and fungusdiseases (E. N. Chernyak), venereal diseases (N. S. Smorodintsev, M. N. Shagalov) and leprosy (N. N. Metlitskiy, A. A. Mikhaylova, M. B. Khudayberdyev, Ya. F. Petel'nik). Docent A. M. Izmaylov is working on resort and climatological therapy of skin diseases, specifically at the Archman resort.

Problems of diagnostics, therapy and prevention of tuberculosis were pursued, up to 1962, by the staff of therapeutic chairs of TGMI, mainly, the chair of faculty therapy, which included a course on phthisiology. Ye. A. Pletnev, A. A. Akhundov, O. T. Tachev, S. O. Ovezov, S. G. Dzhumasakhatov, F. M. Ismailov and others did much research and organizational-methodological work dealing with the control of tuberculosis.

At the present time, scientific research and development of measures for the control of tuberculosis are pursued at the Turkmen Scientific Research Institute of Tuberculosis, docent D. N. Nepesov, director). The main scientific directions of the institute and chair of tuberculosis are epidemiology and organizational aspects of tuberculosis-control measures in TSSR (D. N. Nepesov, O. T. Tachev, S. Kh. Kulish, A. A. Akhundov, S. P. Ovezov, F. A. Rashitova, K. Ch. Charyyev, B. A. Atadzhanov and others), as well as investigation of bacteriology of tuberculosis for the purpose of further refinement of diagnostic methods (O. T. Tachev, T. M. Kim, T. I. Isayeva). Some attention is devoted to the study of extrapulmonary forms of tuberculosis, in particular, to lesions of genitourinary organs (O. T. Tachev, T. M. Kim, L. I. Arutyunov), and pathomorphology of tuberculosis (B. R. Rakhmetov, I. V. Vladykin).

Much organizational work was done to strengthen the material and technical base of the institute, under the supervision of docent D. N. Nepesov, director of the Turkmen Scientific Research Institute of Tuberculosis.

A new stage began in the study of epidemiology, diagnostics, therapy and prevention of malignant neoplasms in the republic with the foundation, in 1963 of the Turkmen Scientific Research Institute of Oncology (Prof S. K. Nuryagdyev, director). The main directions of scientific research here and on the chair of oncology are the study of epidemiology of cancer in TSSR and development of diagnostic laboratory methods for early detection of cancer. The staff of this institute has made definite strides in these areas.

Investigation of the epidemiology of cancer in Ashkhabadskaya, Krasnovodskaya oblasts and major cities of TSSR has been completed (S. K. Nuryagdyev, A. I. Aronskiy, B. G. Mirlin, A. S. Maksimenko and others).

Certain patterns have been established, with regard to localization of cancer in the indigenous and immigrant population, depending on their place of residence (urban or rural). Methods of laboratory diagnostics of cancer have been developed, involving assay of trace elements of blood and neoplastic tissue (R. Dovbayev, B. Kh. Kudratullayeva). The institute is continuing with research on epidemiology and laboratory detection of cancer, by means of using more refined and objective methods.

The Turkmen Republic Center for Medical Information (V. A. Babayants, director) is performing work that is useful to science; it compiles bibliographies dealing with the most important problems of regional pathology. The Center for Medical Information conducts some research, together with the chair of obstetrics and gynecology, urology course, etc.

The scientific medical institutions of the TSSR Ministry of Health are performing much scientific, organizational-methodological, therapeutic and preventive work, while TGMI is additionally involved in pedagogic work. The medical scientists of TSSR have made great strides with respect to introducing scientific advances to practice. Under the 9th Five-Year Plan alone, 92 methodological recommendations and 125 rationalization proposals were prepared and adopted in practice. In 1976, 17 methodological recommendations and 75 rationalization proposals were prepared, 25 seminars, conferences and meetings were held, which dealt with the advances in medical science.

The future tasks for medical science have been clearly spelled out in the decisions of the 25th CPSU Congress and 21st Congress of the Turkmen Communist Party. We need not question the fact that the medical scientists of Turkmenistan will honorably cope with the scientific tasks put to them by the Communist Party and government of the Soviet Union.

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PUBLIC HEALTH

DEVELOPMENT OF THE NETWORK OF THE SANITARY AND EPIDEMIOLOGICAL SERVICE IN TURKMEN SSR

Ashkhabad ZDRAVOOKHRANENIYE TURKMENISTANA in Russian No 11, 1977 pp 17-20

[Article by D. B. Tesler and I. R. Dzhapbarov]

[Text] The Soviet people are celebrating the 60th anniversary of the Great October Socialist Revolution in an atmosphere of great political and industrial enthusiasm, inspired by the historical decisions of the 25th CPSU Congress, the decision of the Plenum of the Central Committee CPSU (May 1977) and discussion of the draft of the USSR Constitution.

In the years of Soviet power, public health has become an organic element of the entire building of socialism, since concern about safeguarding and constantly improving the health of the people was one of the most important objectives in the activities of the Communist Party and Soviet State.

Along with the entire nation, there was also growth and strengthening of the health service in this republic. Following in the steps of the Russian Federation, the government of Turkmen SSR adopted the decree "On health agencies of the republic" on 8 August 1926, which summarized the knowhow of 5 years of operation of public health agencies and posed several major tasks.

The range of functions of health agencies included the following: protection of the environment, housing, foods, organization of epidemic-control measures, control of social diseases, child health care, health statistics, health education, involvement in solving problems of sanitary protection of labor. This document defined the number of personnel required, based on the administrative division of the republic existing at that time: 10 health inspectors (physicians) in the okrugs [districts], 6 in cities and 1 in the system of Narkomzdrav [People's Commissariat of Health].

The decree adopted by SNF [Council of People's Commissars] on 23 December 1933, entitled "All-Union State Health Inspection," was an important step forward in developing the health service. Accordingly, State health inspectorates were opened in six cities of the republic, which had inter-rayon functions, and the positions of rayon inspectors were added, the duties of which included surveillance of sanitation of populated areas and involvement in elaborating measures to improve them.

The sanitary and epidemiological service had negligible personnel resources, no material and technical base and was limited, in essence, to organization of epidemic control measures. Organization of bath houses and washing facilities were among the measures implemented at this stage.

Sanitary and epidemiological stations [SES] began to be opened in Turkmenia in 1935. By the end of 1937, there were 5 such stations and 9 sanitary bacteriological laboratories employing 18 state sanitary and health inspectors. By the end of 1939, there were 28 SES in the republic.

Under the first few five-year plans, the health agencies were involved in developing the plan for supplying water to western Turkmenia, expansion of the network of bath houses and sanitary disinfection centers. By the end of the term of the second Five-Year Plan, there was regular chlorination of the water in Ashkhabad, Krasnivodsk, Bayram-Ali and Gasan-Kuli.

In 1937, health inspection of food was organized. At the suggestion of the health agencies, the government of the republic adopted several important decisions pertaining to putting order in enterprises of the fish and meat industry. Salt intake was established for the workers of some industrial enterprises, and ventilation systems were equipped in the silk-spinning shops of silk-reeling factories.

Under the third Five-Year Plan, bacteriological and the first sanitary chemical laboratories were opened. The SES have been pursuing hygienic research in their laboratories since 1951.

The documents that determined further refinement of health legislation and the system of management of the sanitary and epidemiological service was the decree dated 30 October 1963, "On State sanitary surveillance in the USSR," and the ensuing decree adopted by Turkmen SSR on 7 Feb 1964. These decrees provided for strengthening the sanitary and epidemiological service, improving material and technical equipment, definition of rights, differentiated duties of agencies and institutions of this service. All this was aimed at upgrading the work. SES began to make wider use of laboratory tests.

After 1963, the Turkmen Ministry of Health devoted special attention to strengthening of the laboratory base of the sanitary and epidemiological service: outfitting it with furniture, noise gages, analytical balances, various aspirators, gas analyzers, etc. This made it possible for the SES to perform 100 different tests: thin-layer chromatography, integral studies of polymers and plastics, spectral analysis, new physicochemical studies and to expand the volume of bacteriological studies.

Some of the SES used the method of simultaneous inspection of similar objects, which reduced the time required to perform such examinations and relieved health inspectors' assistants from superfluous technical work, and specialists acquired skill in summarizing material. Reports on sanitary inspection were prepared and submitted annually to rayon and municipal SES.

Further refinement of surveillance quality was related to the change to a new structure and staffing, in accordance with an order issued by the USSR Minister of Health on 29 April 1969. The number of health inspector positions was increased by 1.5 times, that of laboratory technicians with higher education by 2.5 times and laboratory technicians with secondary education, by 4 times. A total of 12 new chemical specialized laboratories was opened, including some toxicological ones for demonstration of residual levels of toxic chemicals and laboratories of physicochemical investigative methods.

The staff of 30 rayon SES was increased by two technicians. The structure of the SES was based on the principle of a single department, which made it possible to make rational use of the base and personnel, as well as further improve a number of work indices. Public [volunteer] sanitary inspectors began to be used on a wider scale in sanitary inspection work, and this relieved the personnel in the sanitary service from work that did not require special qualifications. A centralized laboratory was organized in Chardzhouskaya Oblast on a trial basis.

The intensive rate of development of technological progress in all branches of the national economy made it necessary to adopt a new statute on State sanitary inspection in the USSR, which was adopted and approved by the USSR Council of Ministers on 31 May 1973, and which stipulated that there should be expansion of the range of activity of the sanitary and epidemiological service, legislated control over the use of polymers and plastics, growth stimulators, introduction of new processes, instruments and equipment in industry, use of radioactive, toxic and potent substances, chemical agents for the protection of plants, with reflection of measures dealing with the prevention, abatement and elimination of noise. There was more comprehensive elaboration of problems of environmental protection.

The sanitary service entered a new stage of development, a stage of deeper work. The agencies of the State sanitary inspectorate were oriented toward continued improvement of work quality and effectiveness.

The entire process of inception and development of the sanitary and epidemiological service in this republic was associated with development and refinement of its laboratory departments, since it is only on the basis of the results of objective tests that health inspectors can develop with substantiation and implement ameliorative measures and assess their efficacy. All this resulted in an increase in scope of hygienic studies.

Problems of preventive sanitary inspection, which is one of the main measures implemented by the republic's sanitary service, are being solved. In 1976 alone, more than 1000 opinions were issued pertaining to all cation of areas, blueprints were examined for over 300 projects, including 60 industrial enterprises, about 10 general plans for cities and villages of the urban type, and 1200 projects under construction were inspected. The sanitary service was involved in the introduction of more than 700 new

technological processes and formulas; there was consideration and approval of new technological conditions and republic standards.

The number of inspections increased by 5000, which meant that projects were visited more frequently. The number of sanitary and hygienic studies increased by 70,000. This, in turn, resulted in an increase in inspections involving the use of objective examination methods.

As a result of more intensive supervision and adoption of administrative measures, the sanitary state of a number of projects improved; 120 facilities were improved with respect to hygiene of nutrition, 47 facilities were brought up to the existing standards of industrial hygiene and 60 were brought up to those of municipal hygiene.

In the years of Soviet power, there has been total eradication in this republic of dangerous infectious diseases, parasitic typhus and smallpox; more recently, such serious diseases as malaria and trachoma have disappeared, and poliomyelitis and diphtheria are being eradicated. The offensive against other infections is also continuing, and preventive measures play the first and foremost role in controlling them, their necessity having been mentioned already by V. I. Lenin.

The scientists of Turkmen SSR, which enlisted all forces for the prevention and control of infectious diseases in the early years of its development, made the utmost contribution to public health practices.

In the early years of existence of the Turkmen Institute of Epidemiology and Microbiology (1929), its activities were directed toward the prevention of the most widespread infectious, parasitic diseases and particularly dangerous infections, and later on, on the production of bacterial and viral products.

Research on intestinal infections is being conducted in the most orderly way. V. D. Timakov and V. V. Suknev, in collaboration with the staff of the institute, conducted research on "avisceral" forms of *S. typhosa*, worked on development of more effective vaccines against typhoid fever, as well as on improving diagnostics of intestinal infections. Extensive studies were pursued of dysentery, leishmaniasis and malaria.

Considerable attention has been devoted to investigation of the biology of the pathogen of scarlet fever, the hemolytic streptococcus, since the 1950's.

After the institute was renamed as the Ashkhabad Scientific Research Institute of Epidemiology and Hygiene in 1953 and its merger with the Institute of Malaria and Parasitology in 1956, there was expansion of the volume of scientific research. Research is continuing on ancylostomiasis, ascariasis, trichuriasis and epinococcosis, hymenolepiasis, as well as nosogeography of helminthiasis and serological diagnostics thereof. In the early 1960's, research on salmonellosis began. The problem of infectious hepatitis is being given much attention by the institute in recent years. Research on hygiene of nutrition made a contribution to science; much attention is being

devoted to the quality of water in the Karakumy Canal, self-purification thereof, contamination with pathogenic pathogens, and the role in formation of the epidemic process referable to typhoid fever and paratyphus.

All of the research done at the institute is closely related to the distinctions of this republic, its climate, sociohygienic life style of the people, regional pathology, and this aided in developing specific measures to lower the morbidity rate and ameliorate the environment.

The 25th Congress of the CPSU has put to the workers of the sanitary service some new tasks dealing with prevention and further lowering of incidence of infectious and occupational diseases, development and adoption of hygienic standards in all branches of the national economy, aimed at ameliorating the environment and improving working and living conditions. There are plans for continued refinement of organizational measures, institution at the oblast SES of teams dealing with protection of atmospheric air, acoustic laboratories and laboratories of industrial physiology.

The complex measures dealing with refinement of the organizational basis of the sanitary and epidemiological service, which provide for introduction to practice of scientific achievements in this field, will make it possible to implement the directives of the Party and government in the area of continued development of the preventive direction of Soviet public health.

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